VOLUME 108 (1) — JANUARY 1999

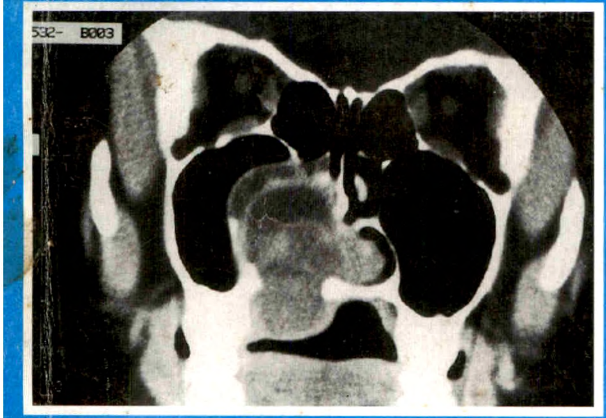
CUK-H03725-47-P024702

47

— Founded in 1892 —

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

Official Organ of the
AMERICAN LARYNGOLOGICAL ASSOCIATION
AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATIO



MAKE YOUR DIAGNOSIS. SEE PAGE 92.

EXPERIMENTAL APPROACHES TO VOCAL FOLD ALTERATION: INTRODUCTION TO THE MINITHYROTOMY

ECTASIAS AND VARICES OF THE VOCAL FOLD: CLEARING THE STRIKING ZONE

ENDOSCOPIC MIDDLE EAR SURGERY

TITANIUM VOCAL FOLD MEDIALIZING IMPLANT: INTRODUCING A NOVEL IMPLANT SYSTEM FOR EXTERNAL VOCAL FOLD MEDIALIZATION

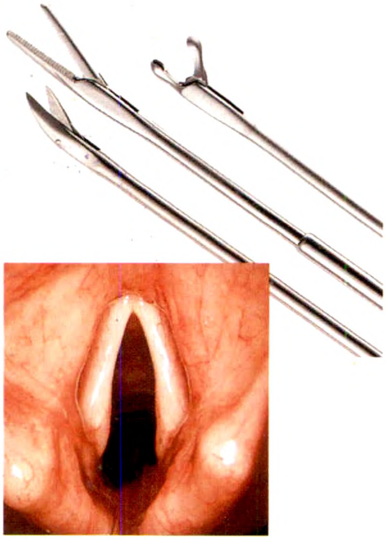
OPTICAL TRACKING OF A MICROSCOPE FOR IMAGE-GUIDED INTRANASAL SINUS SURGERY

ANNALS
PUBLISHING CO.
ST. LOUIS

WEB SITE — http://www.Annals.com

Laryngoscopes from Karl Storz

For all anatomic situations



Designed in collaboration with leading authorities, Karl Storz laryngoscopes provide optimal site specific or panoramic visualization for even the most difficult anatomic situations. From neonate to adult, these lightweight stainless steel laryngoscopes have a unique handle for easy introduction. The Kantor-Berci Video Laryngoscope provides a distal telescopic view and allows unobstructed bi-manual manipulations from the monitor image. HOPKINS rod-lens telescopes from 0° to 120° enhance the diagnostic capability of direct laryngoscopy.

For more information or a demonstration, please contact your local Karl Storz representative, or call Karl Storz directly at **(800) 421-0837.**

KARL STORZ GmbH & Co.
Mittelstraße 8, D-78532 Tuttlingen, Germany
Postfach 230, D-78503 Tuttlingen, Germany
Telefon: (07461) 70 80
Telefax: (07461) 70 81 05

KARL STORZ Endoscopy-America, Inc.
600 Corporate Pointe
Culver City, CA 90230-7600
Telephone: (310) 338-8100
(800) 421-0837
Telefax: (310) 410-5530

KARL STORZ Endoscopy-Canada, Inc.
438 University Avenue, Suite 1800
Toronto, Ontario, Canada M5G 2K8
Telephone: (416) 596-9900
(800) 268-4880 (English)
(800) 361-7388 (Francais)
Telefax: (416) 596-9333

KARL STORZ Endoscopia Latino America
815 N.W. 57th Ave., Ste. No. 480
Miami, FL 33126-2042, USA
Telefono: (305) 262-8980
Telefax: (305) 262-8986

E-mail: karlstorz-marketing@karlstorz.de
Internet: http://www.karlstorz.de
http://www.karlstorz.com

STORZ
Karl Storz Endoscopy
www.karlstorz.com

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

— Founded in 1892 —

47

Editor

BRIAN F. McCABE, MD
Iowa City, Iowa

Associate Editors

CHARLES D. BLUESTONE, MD
Pittsburgh, Pa
GEORGE A. GATES, MD
Seattle, Wash

LAWRENCE W. DeSANTO, MD
Scottsdale, Ariz
LEE A. HARKER, MD
Omaha, Neb

Board of Editors

JOHN G. BATSAKIS, MD	Kalkaska, Mich
JOEL M. BERNSTEIN, MD, PhD	Buffalo, NY
ANDREW BLITZER, MD, DDS	New York, NY
DERALD E. BRACKMANN, MD	Los Angeles, Calif
POUL BRETLAU, MD, DMSc	Copenhagen, Denmark
RICHARD A. BUCKINGHAM, MD	Park Ridge, Ill
RICHARD A. CHOLE, MD, PhD	St. Louis, Mo
JACK D. CLEMIS, MD	Chicago, Ill
CHARLES W. CUMMINGS, MD	Baltimore, Md
PATRICK J. DOYLE, MD	Vancouver, Canada
ALFIO FERLITO, MD	Udine, Italy
UGO FISCH, MD	Zurich, Switzerland
BRUCE GANTZ, MD	Iowa City, Iowa
JEFFREY P. HARRIS, MD, PhD	San Diego, Calif
GERALD B. HEALY, MD	Boston, Mass
WILLIAM F. HOUSE, MD	Los Angeles, Calif
STEVEN K. JUHN, MD	Minneapolis, Minn
TIMOTHY T. K. JUNG, MD, PhD	Loma Linda, Calif
JEROME O. KLEIN, MD	Boston, Mass
FRANK E. LUCENTE, MD	New York, NY
WILLIAM L. MEYERHOFF, MD, PhD	Dallas, Tex
JOSEF MILLER, PhD	Ann Arbor, Mich
AAGE R. MØLLER, PhD	Dallas, Tex
WILLIAM W. MONTGOMERY, MD	Boston, Mass
EUGENE N. MYERS, MD	Pittsburgh, Pa
YASUYA NOMURA, MD	Tokyo, Japan
LORNE S. PARNES, MD	London, Canada
FRANK N. RITTER, MD	Ann Arbor, Mich
ROBERT J. RUBEN, MD	Bronx, NY
JAI H. RYU, PhD	Winston-Salem, NC
JACOB SADÉ, MD	Tel Aviv, Israel
ISAMU SANDO, MD	Pittsburgh, Pa
CLARENCE T. SASAKI, MD	New Haven, Conn
RICHARD J. H. SMITH, MD	Iowa City, Iowa
HEINZ R. STAMMBERGER, MD	Graz, Austria
LESTER D. R. THOMPSON, MD	Washington, DC
JAN E. VELDMAN, MD, PhD	Utrecht, The Netherlands
BRUCE M. WENIG, MD	Washington, DC
T. J. YOO, MD, PhD	Memphis, Tenn

Software Review and Computer Applications Editor

KEVIN T. KAVANAGH, MS, MD	Somerset, Ky

Imaging Editor

YUTAKA SATO, MD	Iowa City, Iowa

Book Review Editor

DENNIS G. PAPPAS, MD	Birmingham, Ala

Emeritus Board Members

WESLEY H. BRADLEY, MD	Albany, NY
D. THANE CODY, MD	Jacksonville, Fla
SEYMOUR COHEN, MD	Los Angeles, Calif
ARNDT J. DUVALL III, MD	Minneapolis, Minn
JOHN M. FREDRICKSON, MD	St Louis, Mo
RICHARD R. GACEK, MD	Syracuse, NY
JEROME C. GOLDSTEIN, MD	Alexandria, Va
SIR DONALD F. N. HARRISON, MD PhD	London, England
SAM E. KINNEY, MD	Cleveland, Ohio
JOHN A. KIRCHNER, MD	New Haven, Conn
DAVID J. LIM, MD	Los Angeles, Calif
FRED H. LINTHICUM, Jr, MD	Los Angeles, Calif
MICHEL PORTMANN, MD	Bordeaux, France
LORING W. PRATT, MD	Waterville, Me
WILLIAM H. SAUNDERS, MD	Columbus, Ohio
RUEDIGER THALMANN, MD	St Louis, Mo
HARVEY M. TUCKER, MD	Cleveland, Ohio
PAUL H. WARD, MD	Los Angeles, Calif

P24702

OTOLARYNGOLOGIST

Board-eligible or board-certified otolaryngologist for southeastern Wisconsin practice in underserved area with growing Hispanic population. Practice includes general otolaryngology, head and neck oncologic surgery, endoscopic sinus surgery, laser surgery, and facial-plastic surgery. On call every other night for three local hospitals, every night for practice. Wisconsin license required. Opening is immediate.

Please send curriculum vitae to:

Office Manager
PO Box 580202
Pleasant Prairie, WI 53158

A158

CLINICAL AND RESEARCH FELLOWSHIP IN OTOLOGY AND NEUROTOLOGY

MASSACHUSETTS EYE AND EAR INFIRMARY

Fellowship training is offered for individuals who aspire to a full-time academic career. Two- and three-year fellowships are available. Three-year fellowships provide additional opportunities for basic research training, while the two-year fellowship will provide opportunities for clinical research. Board eligibility or certification is required.

For more information, contact:

Michael J. McKenna, MD
Dept of Otolaryngology
Massachusetts Eye and Ear Infirmary
243 Charles Street
Boston, MA 02114
(617) 573-3654

A2

3rd International Conference on Acoustic Neurinoma and Other CPA Tumors

Rome (Italy) 12-16 June 1999
Cavalieri Hilton Hotel

Organized by
Mario Sanna M.D.

MAIN TOPICS

A) ACOUSTIC NEURINOMA

B) OTHER CPA TUMORS

1) Meningiomas of the CPA
2) Petrous Bone Meningiomas extended to the CPA
3) Paragangliomas extended to the CPA
4) Jugular Foramen Schwannomas
5) Lipomas of CPA
6) Petroclival Meningiomas
7) Epidermoids

SCIENTIFIC SECRETARIAT

Taibah A. M.D., Russo A. M.D., Mancini F. M.D.
Via Emmanueli, 42 - 29100 PIACENZA (Italy) - Tel. ++39-523.754362 - Fax ++39-523.453708
E-mail: neurinoma.sanna@otologicgr.inet.it - http://www.netline.it/otologicgr

MEDICINA VIVA ORGANIZING SECRETARIAT

V.le dei Mille, 140 - 43100 PARMA (Italy) - Tel. ++39-521.290191 - Fax ++39-521.291314-293264
E-mail: medicina.viva@rsadvnet.it - http://www.rsadvnet.it/medicinaviva

MICROVASCULAR AND FACIAL NERVE ANASTOMOSIS

PRIVATE COURSE

(Fresh Cadaveric and Anesthetized Specimens)

Private Scheduling 4 Days

Brookwood Medical Center
Department of Microsurgery

Fee: $2,500

Address inquiries to:

Dennis G. Pappas, Jr, MD
Pappas Ear Clinic
2937 Seventh Ave S
Birmingham, AL 35233
(205) 324-6925
Fax (205) 254-3013

A156

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

— Founded in 1892 —

EDITOR'S OFFICE

Brian F. McCabe, MD
Department of Otolaryngology –
Head & Neck Surgery
University Hospitals & Clinics
Iowa City, IA 52242
(319) 356-2310

BUSINESS OFFICE

Annals Publishing Company
4507 Laclede Avenue
St Louis, MO 63108
(314) 367-4987
Fax (314) 367-4988
E-mail: manager@Annals.com

STAFF

Managing Editor
Michol L. Sheridan

Business Manager
Kenneth A. Cooper, Jr

Chief Copyeditor
Edna Hayes Harrison

Copyeditor
Kirsten K. Novak

Circulation Manager
Michelle M. Steuerwald

Editorial Assistant
Timothy I. Watt

ADVERTISING REPRESENTATIVES

— East & Midwest —
Cunningham Associates
180 Old Tappan Rd
Old Tappan, NJ 07675
(201) 767-4170
Fax (201) 767-8065

— West —
Charles B. Healy
PO Box 5213
Palm Springs, CA 92263
(760) 320-0118
Fax (760) 325-5473

EDITORIAL CONTENT

The *ANNALS* publishes original manuscripts of clinical and research importance in otolaryngology – head and neck medicine and surgery, bronchoesophagology, head and neck oncology and surgery, plastic and reconstructive surgery, pediatric otolaryngology, audiology, speech pathology, and related specialties. In-depth studies (supplements), papers of historical interest, computer software reviews and applications in otolaryngology are also published, as well as imaging, pathology, and clinicopathology studies, book reviews, and letters to the editor. All papers and supplements are peer-reviewed. The *ANNALS* is the official journal of the American Laryngological Association and the American Broncho-Esophagological Association.

SUBSCRIPTIONS

1999 Annual Subscription Rates	*USA*	*International Surface Mail (All Regions)*
Institution*	$179.00	$204.00
Individual†	125.00	150.00
Resident/Student†	82.00	98.00

*Institutional (multiple-reader) subscription rates apply to public and private libraries, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and commercial and private institutions and organizations.

†Individual, resident, and student subscriptions must be in the individual's name and must be billed to and paid for by the individual.

Airmail rates are available upon request.

CLAIMS

Claims for missing issues must be received within 60 days of the month of publication for the United States and Canada, and 180 days for other countries. Single copy prices will be charged on missing issues claimed after that date.

BACK ISSUES

A comprehensive inventory of back issues and supplements is available. Prices are furnished on request.

CHANGE OF ADDRESS

Address changes must be received 45 days prior to the effective date so that the subscription will be received without interruption.

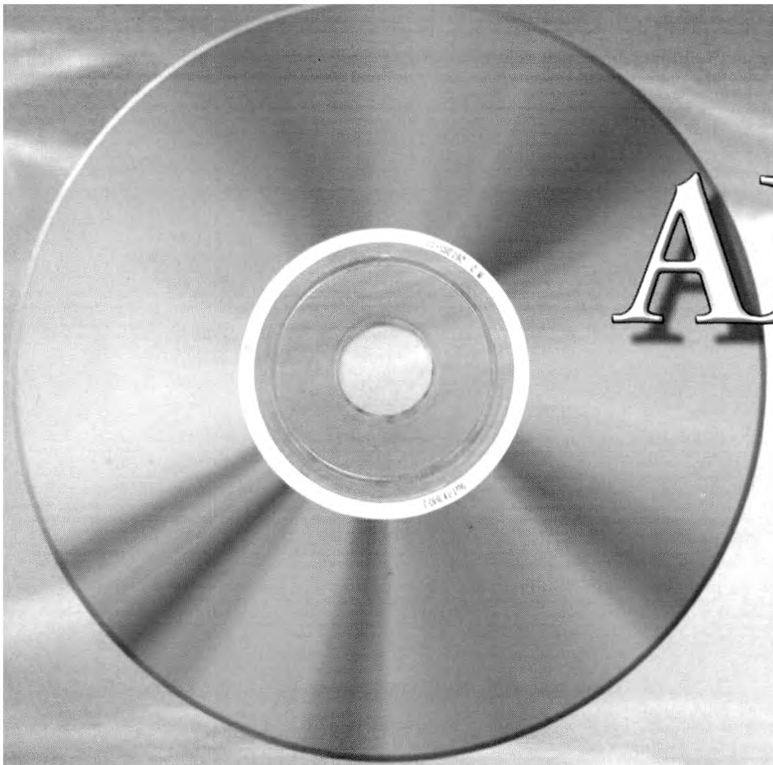
MICROFILM

The *ANNALS* is available in microform from University Microfilms International, 300 North Zeeb Road, Ann Arbor, MI 48106.

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Periodicals postage paid at St Louis, Mo. POSTMASTER: Send address changes to *ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY*, c/o Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108-2103.

Printed on acid-free paper

COPYRIGHT© 1999, ANNALS PUBLISHING COMPANY



ANNALS

The brand-new CD-ROM from the *Annals of Otology, Rhinology & Laryngology* contains the whole 1998 volume on one handy disk.

ANNAL'S convenient CD-ROM gives you:

- Instant access to the total editorial content, references, abstracts, tables and illustrations — the most compelling research at your fingertips
- Advanced search and retrieval
- Hypertext links for obtaining information
- An easy way to print out full articles

Order Form

Yes! Send my charter edition of *ANNALS* on CD-ROM, which includes the calendar year of January–December 1998. *(Please print.)*

Name ______________________________

Address ______________________________

City ____________ State ____________ ZIP ____________

Country ____________ Telephone (____) ____________

E-mail ______________________________

I enclose payment (payable in US dollars):

Current Subscribers	☐ $ 69.95 (Individual)	☐ $ 99.95 (Institutional)
Non-current Subscribers	☐ $174.95 (Individual)	☐ $249.95 (Institutional)

Add $5.95 for Shipping and Handling

☐ Payment enclosed ☐ Visa ☐ Mastercard ☐ Bill me

Card No. ____________ Expiration Date ____________

Signature ______________________________

Fax to (314) 367-4988 or mail to *ANNALS* PUBLISHING COMPANY, 4507 LACLEDE AVENUE, ST. LOUIS, MO 63108, U.S.A.

E-mail: Manager@Annals.com • http://www.annals.com

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

VOLUME 108 JANUARY 1999 NUMBER 1

CONTENTS

FROM THE AMERICAN LARYNGOLOGICAL ASSOCIATION

Experimental Approaches to Vocal Fold Alteration: Introduction to the Minithyrotomy
Steven D. Gray, MD; Steven A. Bielamowicz, MD; Ingo R. Titze, PhD; Heather Dove, MA; Christy Ludlow, PhD 1

Ectasias and Varices of the Vocal Fold: Clearing the Striking Zone
Ilan Hochman, MD; Robert T. Sataloff, MD, DMA; Robert E. Hillman, PhD; Steven M. Zeitels, MD 10

Ablation of Teflon Granulomas in the Canine Larynx With the Free-Electron Laser
Charles F. Lano, Jr, MD; Lou Reinisch, PhD; Robert H. Ossoff, DMD, MD; C. Gaelyn Garrett, MD; Timothy Kuo; G. Lee Bryant, Jr, MD; Jay A. Werkhaven, MD 17

Transverse Infrahyoid Approach to Bilateral Glottic Tumors
Anthony J. Reino, MD, MSc; William Lawson, MD, DDS; Hugh F. Biller, MD 24

OTOLOGY AND AUDIOLOGY

Immunologic and Histologic Observations in Reovirus-Induced Otitis Media in the Mouse
Robert B. Meek III, MD; Benjamin M. McGrew, MD; Christopher F. Cuff, PhD; Albert S. Berrebi, PhD; George A. Spirou, PhD; Stephen J. Wetmore, MD 31

Endoscopic Middle Ear Surgery
Muaaz Tarabichi, MD 39

Application of Labeling Techniques to Archival Temporal Bone Sections
Qing Tian, MD; Fred H. Linthicum, Jr, MD; Elizabeth M. Keithley, PhD 47

RHINOLOGY AND AIRWAY

Optical Tracking of a Microscope for Image-Guided Intranasal Sinus Surgery
Rolf Hauser, MD; Birgit Westermann, MSc, PhD 54

Manometric Study of Paranasal Sinus Mucoceles
Erik S. Kass, MD; Richard L. Fabian, MD; William W. Montgomery, MD 63

Radiographic Evaluation of Children With Nasopharyngeal Obstruction Due to the Adenoid
Yusuf K. Kemaloglu, MD; Nebil Goksu, MD; Erdogan Inal, MD; Necmettin Akyildiz, MD 67

LARYNGOLOGY AND HEAD AND NECK

Changes in Head and Neck Tumor Hypoxic Fraction During Split-Course Radiochemotherapy
Rainer Jund, MD; Horst-Jürgen Feldmann, MD; Barbara Wollenberg, MD;
Peter Stadler, MD; Michael Molls, PhD 73

Titanium Vocal Fold Medializing Implant: Introducing a Novel Implant System for External Vocal Fold Medialization
Gerhard Friedrich, MD 79

Carotid Artery Occlusion Due to Bacterial Paranasal Sinusitis
Mehmet Ziya Özüer, MD; Fazil Necdet Ardiç, MD; Erdal Coskun, MD;
A. Nevzat Yalçin, MD; Nuran Sabir Akkoyunlu, MD 87

IMAGING CASE STUDY OF THE MONTH

Brown Tumor of the Palate in a Patient With Primary Hyperparathyroidism
Shaun N. Scott, MD; Scott M. Graham, MD; Yutaka Sato, MD;
Robert A. Robinson, MD, PhD 91

CLINICOPATHOLOGICAL CONSULTATION

AIDS-Related Plasmablastic Lymphomas of the Oral Cavity and Jaws: A Diagnostic Dilemma
Antonino Carbone, MD; Gianluca Gaidano, MD; Annunziata Gloghini, PhD;
Alfio Ferlito, MD; Alessandra Rinaldo, MD; Harald Stein, MD 95

MISCELLANEOUS

Book Review 100

Information for Subscribers 3a

Instructions to Authors 7a

Index to Advertisers 12a

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

VOLUME 108 FEBRUARY 1999 NUMBER 2

CONTENTS

PART 1

FROM THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

Histopathology of Congenital Subglottic Stenosis
Lauren D. Holinger, MD ... 101

Effect of Intravenous Substance P on Laryngeal Adductor Activity in Young Dogs
Nancy M. Bauman, MD; DeQiang Wang, MD; Debra M. Jaffe, MD;
Anthony D. Sandler, MD; Erich S. Luschei, PhD ... 112

Histomorphometric and Laryngeal Videostroboscopic Analysis of the Effects of Corticosteroids on Microflap Healing in the Dog Larynx
John R. Coleman, Jr, MD; Shane Smith, MD; Lou Reinisch, PhD;
Cheryl R. Billante, PhD; Jacob P. Ossoff; Walter Deriso; C. Gaelyn Garrett, MD ... 119

INDEPENDENT CONTRIBUTIONS

Radiotherapy Followed by Neck Dissection for Small Head and Neck Cancers With Advanced Cervical Metastases
Steven J. Wang, MD; Marilene B. Wang, MD; Thomas C. Calcaterra, MD ... 128

Clinical Applications of Transiently Evoked Otoacoustic Emissions in the Pediatric Population
Sukgi S. Choi, MD; Irene A. Pafitis, PhD; George H. Zalzal, MD;
Gilbert R. Herer, PhD; Kantilal M. Patel, PhD ... 132

Smoking Increases Facial Skin Flap Complications
John B. Kinsella, FRCS(Edin); Christopher H. Rassekh, MD;
Zachary D. Wassmuth, MD; James A. Hokanson, PhD; Karen H. Calhoun, MD ... 139

Autotransplantation of the Trachea: Experimental Evaluation of a Reconstructive Technique for Extended Hemilaryngectomy Defects
Pierre R. Delaere, MD, PhD; Vincent Vander Poorten, MD, MSc; Robert Hermans, MD ... 143

Transnasal Endoscopic Removal of an Orbital Cavernoma
Philippe Herman, MD, PhD; Guillaume Lot, MD; Bénédicte Silhouette, MD;
Rémi Marianowski, MD; Frédéric Portier, MD; Michel Wassef, MD; Patrice Tran Ba Huy, MD ... 147

Patients With CHARGE Association: A Model to Study Saccular Function in the Human
Jean-Philippe Guyot, MD; Dominique Vibert, MD ... 151

Carbon Dioxide Laser Microsurgery of Benign Vocal Fold Lesions: Indications, Techniques, and Results in 251 Patients
Marc Remacle, MD, PhD; Georges Lawson, MD; Jean-Baptiste Watelet, MD ... 156

Telescopic Video Microlaryngeal Surgery
Albert ReMing Yeh, MD; Hung-Meng Huang, MD; Yu-Lin Chen, MD 165

Specific Immunoglobulin E, Interleukin-4, and Soluble Vascular Cell Adhesion Molecule–1 in Sera in Patients With Seasonal Allergic Rhinitis
Tateo Masamoto, MD; Yoshihiro Ohashi, MD; Yoshiaki Nakai, MD 169

Diagnostic and Therapeutic Approach to Migrating Foreign Bodies
Lincoln W. J. Chee, MD, FRCS; Dharambir S. Sethi, MD, FRCS 177

Astrocyte Reaction in the Rat Vestibular Nuclei After Unilateral Removal of Scarpa's Ganglion
Hongyan Li, MD, PhD; Donald A. Godfrey, PhD; Allan M. Rubin, MD, PhD 181

Diagnostic and Therapeutic Management of Bilateral Carotid Artery Occlusion Caused by Near-Suicidal Hanging
Wolfgang Maier, MD; Milo Fradis, MD; Shelton Malatskey, MD; Annette Krebs, MD 189

Decrease of Serum Levels of Soluble CD23 During Immunotherapy in Patients With Perennial Allergic Rhinitis
Ayaki Tanaka, MD; Yoshihiro Ohashi, MD; Yoshiaki Nakai, MD 193

Patulous Eustachian Tube in Long-Term Survivors of Nasopharyngeal Carcinoma
Po-Wen Cheng, MD; Yi-Ho Young, MD; Pei-Jen Lou, MD 201

Successful Treatment of an Invasive Aspergillosis of the Skull Base and Paranasal Sinuses With Liposomal Amphotericin B and Itraconazole
Michael Streppel, MD; Gregor Bachmann, MD; Georg Arnold, MD;
Michael Damm, MD; Eberhard Stennert, MD 205

Vasomotor Rhinitis Following Trauma to the Nose
Samuel Segal, MD; Nathan Shlamkovitch, MD; Ephraim Eviatar, MD;
Leonard Berenholz, MD; Shlomo Sarfaty, MD; Alexander Kessler, MD 208

IMAGING CASE STUDY OF THE MONTH

Multiple Myeloma Presenting as Proptosis
Christopher Ryder, MD; Robert M. Naclerio, MD 211

CLINICOPATHOLOGICAL CONSULTATION

Laryngeal Pathology in the Acquired Immunodeficiency Syndrome: Diagnostic and Therapeutic Dilemmas
Thomas A. Tami, MD; Alfio Ferlito, MD; Alessandra Rinaldo, MD;
Kelvin C. Lee, MD; Bhuvanesh Singh, MD 214

MISCELLANEOUS

Information for Subscribers 5a

Index to Advertisers 8a

PART 2

Diagnosis and Treatment of Acute Otitis Externa. An Interdisciplinary Update .... Supplement 176

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

VOLUME 108 MARCH 1999 NUMBER 3

CONTENTS

FROM THE AMERICAN LARYNGOLOGICAL ASSOCIATION

Virtual Laryngoscopy
Marvin P. Fried, MD; Vik M. Moharir, MD; Hiroshi Shinmoto, MD; Abdalmajeid M. Alyassin, PhD; William E. Lorensen, MS; Liangge Hsu, MD; Ron Kikinis, MD 221

Selective Laryngeal Adductor Denervation-Reinnervation: A New Surgical Treatment for Adductor Spasmodic Dysphonia
Gerald S. Berke, MD; Keith E. Blackwell, MD; Bruce R. Gerratt, PhD; Andrew Verneil, MD; Katherine S. Jackson, RN; Joel A. Sercarz, MD 227

Morphology of the Human Larynx During the First Five Years of Life Studied on Whole Organ Serial Sections
Hans Edmund Eckel, MD; Juergen Koebke, PhD; Christian Sittel, MD; Georg Mathias Sprinzl, MD; Claus Pototschnig, MD; Eberhard Stennert, MD 232

Hypoglossal Nerve Transfer for Laryngeal Reinnervation: A Preliminary Study
Randal C. Paniello, MD; Patty Lee, MD; J. David Dahm, MD 239

OTOLOGY AND AUDIOLOGY

Expression Pattern of the Plasminogen Activator–Plasmin System in Human Cholesteatoma
Matthias P. Schönermark, MD; Peter R. Issing, MD; Birte K. Erbrich, MD; Thomas Lenarz, MD 245

Rare Middle Ear Anomaly in a Patient With Turner's Syndrome
Abdul Razak Rahman Hamzah, MBBS; Mohamed Amin Jalaluddin, FRCS; Rajagopalan Raman, MS 253

Murine Model of Autoimmune Hearing Loss Induced by Myelin Protein P0
Hiroshi Matsuoka, MD; Kuang-Chuan Cheng, PhD; Marc S. Krug, PhD; Yoshiro Yazawa, MD; Tai-June Yoo, MD, PhD 255

Three-Dimensional Quantification of "Still" Points During Normal Facial Movement
Susan E. Coulson, MAppSc; Glen R. Croxson, MBBS, FRACS; Wendy L. Gilleard, MSc 265

Multifocal Cholesteatoma of the External Auditory Canal Following Blast Injury
Michael Wolf, MD; Lela Megirov, MD; Jona Kronenberg, MD 269

Vestibular Responses of Normal and Hydropic Ears of the Guinea Pig to Middle Ear Pressure Application
Yasuhiko Sakikawa, MD; Conrad Wall III, PhD; Robert S. Kimura, PhD 271

Rat Eustachian Tube and Its Musculature
Jef J. S. Mulder, MD; Wim Kuijpers, PhD 277

LARYNGOLOGY AND HEAD AND NECK

Effect of Thyroplasty on Laryngeal Airflow
Janice D. Janas, MD; Pat Waugh, MS; Erik R. Swenson, MD; Allen Hillel, MD 286

Immune Response to *Fusobacterium nucleatum* and *Prevotella intermedia* in Patients With Chronic Maxillary Sinusitis
Itzhak Brook, MD, MSc; Paula Yocum, MSc 293

The "Sign of the Rising Tide" During Swallowing Fiberoscopy: A Specific Manifestation of Zenker's Diverticulum
Sophie Périé, MD; Henri-Pierre Dernis, MD; Guy Monceaux, MD;
Bruno Angelard, MD; Jean Lacau St Guily, MD 296

Localization of Zinc in the Rat Submandibular Gland and the Effect of Its Deficiency on Salivary Secretion
Kosuke Ishii, MD; Masami Sato, MD; Masumi Akita, MD; Hiroshi Tomita, MD 300

Effect of Sleep State on the Laryngeal Chemoreflex in Neonatal Piglets
Suzanne S. Cleland-Zamudio, MD; George S. Goding, MD;
Mark Mahowald, MD; Kerri J. Pernell, MS 309

IMAGING CASE STUDY OF THE MONTH

Microbial Extracranial Aneurysm of the Internal Carotid Artery: Complication of Cervical Lymphadenitis
Toshinori Kato, MD, PhD; Kumi Oto, MD; Takashi Endo, MD, PhD;
Junichi Furusho, MD, PhD; Akinobu Iwasaki, MD, PhD;
Yasushi Sasaki, MD, PhD; Yoji Iikura, MD, PhD 314

CLINICOPATHOLOGICAL CONSULTATION

Papillary Squamous Cell Carcinoma Versus Verrucous Squamous Cell Carcinoma of the Head and Neck
Alfio Ferlito, MD; Kenneth O. Devaney, MD; Alessandra Rinaldo, MD;
Mathew J. Putzi, MD 318

MISCELLANEOUS

Information for Subscribers 2a

Index to Advertisers 9a

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

VOLUME 108 APRIL 1999 NUMBER 4

CONTENTS

PART 1

EDITORIAL

What Is "Spontaneous" Cerebrospinal Fluid Rhinorrhea? Classification of Cerebrospinal Fluid Leaks
Gady Har-El, MD 323

OTOLOGY AND AUDIOLOGY

Integrity of the Auditory Pathway in Young Children With Congenital and Postmeningitic Deafness
Thomas P. Nikolopoulos, PhD; Steve M. Mason, PhD;
Gerard M. O'Donoghue, MCh, FRCS; Kevin P. Gibbin, FRCS 327

Measuring the Effects of Meniere's Disease: Results of the Patient-Oriented Severity Index (MD POSI) Version 1
Michael P. Murphy, MD; George A. Gates, MD 331

Study of Systemic Lupus Erythematosus in Temporal Bones
Michihiko Sone, MD; Patricia A. Schachern; Michael M. Paparella, MD;
Noriko Morizono 338

Effects of Epinephrine on Ouabain-Sensitive, K^+-Dependent *p*-Nitrophenylphosphatase Activity in Strial Marginal Cells of Guinea Pigs
Naoyuki Kanoh, MD, PhD 345

Guided Tissue Generation in the Temporal Bone
Gösta Granström, MD, DDS, PhD; Anders Tjellström, MD, PhD 349

RHINOLOGY AND AIRWAY

Endoscopic Sinus Surgery Improves Pulmonary Function in Patients With Asthma Associated With Chronic Sinusitis
Katsuhisa Ikeda, MD; Noriko Tanno, MD; Gen Tamura, MD;
Hideaki Suzuki, MD; Takeshi Oshima, MD; Akira Shimomura, MD;
Seiichiro Nakabayashi, MD; Tomonori Takasaka, MD 355

Double-Blind Comparative Trial of Ciprofloxacin Versus Clarithromycin in the Treatment of Acute Bacterial Sinusitis
Kevin Clifford, MD; Werner Huck, MS; Michael Shan, PhD; Robert Tosiello, MS;
Roger M. Echols, MD; Allen Heyd, PhD; and the Sinusitis Infection Study Group 360

Nasal Nitric Oxide Does Not Control Basal Nasal Patency or Acute Congestion Following Allergen Challenge in Allergic Rhinitis
Philip E. Silkoff, MBBS; Yehuda Roth, MD; Patricia McClean, MSc;
Philip Cole, MD; Jerry Chapnik, MD; Noe Zamel, MD 368

LARYNGOLOGY AND HEAD AND NECK

Anatomic Study for Posterior Medialization Thyroplasty
Hisayoshi Kojima, MD; Shigeru Hirano, MD; Kazuhiko Shoji, MD;
Nobuhiko Isshiki, MD 373

Utility of Radiographs in the Evaluation of Pediatric Upper Airway Obstruction
David L. Walner, MD; Serge Ouanounou, MD; Lane F. Donnelly, MD;
Robin T. Cotton, MD 378

Percutaneous Tracheostomy: A Comprehensive Evaluation
Kris S. Moe, MD; Sandro J. Stoeckli, MD; Stephan Schmid, MD;
Ernest A. Weymuller, Jr, MD 384

Schneiderian Papillomas of the Pharynx
R. Lucian Sulica, MD; Bruce M. Wenig, MD; Richard F. Debo, MD;
Roy B. Sessions, MD 392

Quantitative Study of Germinal Center Area in Normal and Diseased Tonsils Using Image Analysis
Janet L. Gorfien, MA; Robert Hard, PhD; Bernice Noble, PhD;
Linda Brodsky, MD 398

PEDIATRIC OTOLARYNGOLOGY

Severe Combined Immunodeficiency: Otolaryngological Presentation and Management
Rose Mary S. Stocks, MD, PharmD; Jerome W. Thompson, MD, MBA;
Joseph A. Church, MD; Sheila Kun, RN, MS; Erin Simms, MD 403

IMAGING CASE STUDY OF THE MONTH

Endoscopic Management of Lateral Pharyngeal Pouch
Patti C. Huang, MD; Richard L. Scher, MD 408

CLINICOPATHOLOGICAL CONSULTATION

Sinonasal Malignant Lymphomas: A Distinct Clinicopathological Category
Rachel W. Vidal, MD; Kenneth Devaney, MD; Alfio Ferlito, MD;
Alessandra Rinaldo, MD; Antonino Carbone, MD 411

MISCELLANEOUS

Acknowledgment of Reviewers 420

Information for Subscribers 1a

Instructions to Authors 8a

Index to Advertisers 12a

PART 2

Clinical Results With the CLARION® Multi-Strategy™ Cochlear Implant
Mary Joe Osberger, PhD; Dawn Burton Koch, PhD; Editors .... Supplement 177

IOWA BASIC SCIENCE COURSE IN OTOLARYNGOLOGY

A course for otolaryngology residents

Department of Otolaryngology–Head and Neck Surgery
The University of Iowa
Iowa City, Iowa

Head and neck anatomy, under the instruction of Dr Robert Morecraft includes daily anatomical lectures, supervised dissections, and individual assistance each session.

Lectures by specialists from the College of Medicine: Departments of Anesthesia, Dentistry, Dermatology, Internal Medicine, Neurology, Ophthalmology, Otolaryngology, Pathology, Pediatrics, Pharmacology, Radiology, and Surgery. The lecture series will review the following as they apply to otolaryngology: allergy, anatomy, anesthesia, audiology, biochemistry, craniofacial deformities, dentistry, epidemiology, evoked responses, genetics, immunology, instrumentation, nutrition, oncology, pharmacology, physics, physiology, psychoacoustics, radiology, research design, speech pathology, statistics, trauma.

July 6 – August 20, 1999
Fee: $2,175
Openings: Limited

Coordinators: Margaret M. Browning, MD, Richard S. Tyler, PhD, Jay T. Rubinstein, MD

For further information, contact:

Margaret M. Browning, MD
Dept of Otolaryngology–Head and Neck Surgery
University of Iowa Hospitals and Clinics
200 Hawkins Drive, E230 GH
Iowa City, IA 52242-1078
Phone: (319) 358-4351; fax: (319) 356-4547; e-mail: margaret-browning@uiowa.edu

The University of Iowa does not discriminate in its educational programs and activities on the basis of race, national origin, color, religion, sex, age, or disability.

A142

50TH ANNIVERSARY EXTRAORDINARY CONGRESS OF THE SPANISH SOCIETY OF OTORHINOLARYNGOLOGY HEAD AND NECK SURGERY

Madrid, October 24-27, 1999

PRESIDENT: Prof. T. Sacristán Alonso

4 Magistral Conferences - 35 Extraordinary General Sessions - 58 Instruction Courses
25 Workshops - 342 Oral Presentations – 66 Videos – Posters

Topics: Education and Continuing Training in Otorhinolaryngology / Current Trends in Basic and Clinical Research in Otorhinolaryngology / Diagnosis and Treatment of Deafness / Skull Base Surgery / Diagnosis and Treatment of Functional and Structural Laryngeal Disorders / Treatment of Laryngeal and Hypopharyngeal Cancer / Reconstructive and Plastic Surgery in Head and Neck / Non-oncological Endoscopy Surgery / Snoring and Sleep Apnea / Pediatric Otorhinolaryngology / Vestibular Disorders.

International Faculty: Andrea M., Babighian G., Bluestone C.D., Carrau R., Cook T., Cotton R., Cummings C., Chabolle F., Cheesman A., De La Cruz A., Donaldson J., Felippu A., Fisch U., Fraysse B., Freche C., Gameiro Dos Santos A., Gersdorff M., Goepfert H., Goldstein J., Gonzalez Romero A., Helidonis E., Hermann I., Holinger L., Jahnke V., Jenkins H., Johnson J. T., Kennedy D.W., Kotby M.N., Laccourreye O., Lenarz T., Lund V., Luxford W., Mahieu H., Maniglia J., Marcucci L., Maves M., Miyamoto R., Mocellin M., Monnier P., Myers E., Pais Clemente M., Parisier S., Pedersen B., Pinto J.A., Portmann D., Portmann M., Ruenes Fernandez R., Sanchez Marle J.F., Sanna M., Santos Penha R., Schwartzman J.A., Serrano E., Shah J., Snow G., Steiner W., Stennert E., Traissac L., Trinidad Pinedo J., Van Den Broek P., Weber R., Wright D., Zenner H.P.

Deadlines: Abstract submission: May 5, 1999 - Reduced price registration: June 15, 1999

Registration: Participant 450 US $ – Resident 300 US $ – Accompanying Person 165 US $.
The registration includes Instruction Courses, Welcome Cocktail, Spanish "Fiesta," Coffee Breaks and Lunch.

Simultaneous translation English-Spanish / Spanish-English.

Information: S.E.O.R.L.-P.C.F. - C/General Pardiñas 45,1º D - 28001 Madrid, Spain - Tel +34-91-575.93.93 - Fax +34-91-431.26.92, e-mail:seorl@seorl.org - http://www.seorl.org

INSTRUCTIONS TO AUTHORS

SUBMISSION

Send manuscripts to Editor Brian F. McCabe, MD, Department of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242. Original manuscripts dealing with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck medicine and surgery, maxillofacial and plastic surgery, audiology, speech pathology, and related specialties are considered for publication. All materials submitted for publication undergo peer review. All manuscripts must be accompanied by a signed copyright transfer (see "Copyright," below).

Written permission from both senior author and publisher must be provided to the *Annals* in order to republish materials copyrighted elsewhere. Submit this permission with the manuscript.

Papers are scheduled for publication in chronologic order of acceptance. Manuscripts received in improper form require longer production time, which may delay publication. Manuscripts are edited in accordance with the *AMA Manual of Style*, 8th edition (1989), and with the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Ann Intern Med* 1988;108:258-65).

MANUSCRIPT PREPARATION

Limit papers to a size that will make up to no more than six printed pages, figuring three double-spaced typewritten pages of text to one typeset page; see the journal for estimating space required for references, illustrations, and tables. If a manuscript of greater length is accepted for publication by the Editor, all typeset pages over six are charged to the author at the publisher's cost of $150 per page. Submit an original and two copies of the manuscript, typed on white bond paper with margins of at least 25 mm (1 in), double-spaced throughout, including abstract, references, tables, and legends. Use a type size no smaller than 10 points, preferably 12. Begin each component on a new page in the following sequence: title page, abstract, text, acknowledgments, references, tables, and figure legends. Number pages consecutively in the upper right corner, beginning with the title page. Avoid the use of staples.

The author is responsible for all statements in the paper, as approved on the copyedited galley proofs. Alterations made by the author after the paper has been typeset are charged to the author.

Use standard abbreviations given in *Uniform Requirements*. Express all measurements in metric terms; if original measurements were made in another system, include these parenthetically. Plot audiograms according to ISO standards. Use generic names whenever possible.

Title page must include 1) a concise but informative title, worded to facilitate indexing; 2) an abbreviated form of the title to be used as a running head; 3) authors' full names (no more than seven authors are permitted) and no more than two academic degrees per author; 4) department(s) and institution(s) to which the work is attributed, with authors' present affiliations and addresses, if different, separately noted; 5) statement of grant or other support; 6) name and address of author to whom reprint requests should be sent; and 7) name, address, and telephone and fax numbers of corresponding author. Manuscripts that report animal research performed in the United States must carry the following statement on the title page: "This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of __________ University (or institution)."

Abstracts contain no more than 150 words and state the goal of the study, primary procedures, main findings, and principal conclusions.

Key Words, chosen as far as possible from the National Library of Medicine *Medical Subject Headings*, are listed after the abstract.

References, double-spaced, are numbered consecutively in the order in which they are cited in the text. Primary references should be used whenever possible. The author is charged $1.50 for each reference over 30. Use the style of references given in *Uniform Requirements* or a current issue of the *Annals*. Include the names of all authors and the inclusive page numbers of an article. If a manuscript accepted but not yet published is included in the reference list, give the accepting journal's name, followed by "in press." Manuscripts still in review or not yet accepted formally are cited within the text as "unpublished observations." A reference to a personal communication is also placed in the text, accompanied by a date (year). Papers presented at scholarly meetings but not published are considered "unpublished observations." Papers published only in abstract form are listed as references with "[Abstract]" after the title.

Tables should be on separate sheets, numbered consecutively and headed by a concise title. Put explanatory matter in footnotes. Tables are adjuncts to the text and should not repeat material presented therein. The cost of typesetting tables is billed to the author.

Illustrations must be submitted in three complete sets, unmounted. Only professional-quality glossy photographs and black and white line drawings are acceptable. Computer-generated graphs are acceptable only if they are clear and will reproduce well. Letters, numbers, and symbols should be clear and of uniform size throughout, large enough that each item is legible when reduced for publication. Put legends (detailed explanations) to the photographs on a separate page in the manuscript. Affix a label to the reverse side of each illustration indicating figure number, first author's name, and top of the figure. For radiographs, photomicrographs, CT scans, etc, give indications for maximum cropping and labeling on an overlay or photocopy. Cite each figure in the text in consecutive order. Written permission from identifiable subjects is required. The cost of preparing illustrations for publication (sizing to fit journal, and preparation of negatives for printing) is charged to the author without exception. Color illustrations are accepted; cost estimates for color separations and printing are provided on an individual basis. Illustrations should enhance, not repeat, material presented in the manuscript, and should be kept to a minimum.

MANUSCRIPTS ON SOFTWARE REVIEW AND COMPUTER APPLICATIONS

Programs submitted for review must be compatible with an IBM or Macintosh computer, and the author must specify hardware and system requirements. The following operating systems will be supported: MS-DOS; MS-DOS with Windows; and MAC-OS. Submit the software on either a 3.5" or 5.25" disk. If the program is a template, submit also a runtime version of the source program. Software considered for review includes educational software, artificial intelligence software to aid in the diagnosis of otolaryngic disorders, software for logging operations, software to aid in research, and software that addresses specific problems in otolaryngology. Also, manuscripts reviewing software and computer applications relating directly to otolaryngology are considered for publication. See *Ann Otol Rhinol Laryngol* 1991; 100:876 for specific instructions.

SUPPLEMENTS

A manuscript too long for inclusion in the *Annals* (over 12 typeset pages) may be published as a supplement if approved by the Editor. All costs are borne by the author and estimates are provided upon request. Supplements have the advantages of separate identification and rapid publication, but undergo the same critical review as journal articles.

REPRINTS

Rates are quoted when galley proofs are sent to the author. Orders are signed by the author and returned with the proofs.

COPYRIGHT

The following statements should accompany the manuscript, signed by all authors: 1) "This paper has not been published or submitted for publication elsewhere, other than as stated in a separate letter to the Editor." 2) [*For papers with more than one author*] "I have contributed substantively to the development of the content of this paper and have agreed to have my name listed as an author in the final, revised version." 3) "In consideration of the *Annals of Otology, Rhinology & Laryngology* taking action in reviewing and editing my (our) submission, I hereby transfer, assign, or otherwise convey all copyright ownership to the Annals Publishing Company in the event such work is published in the *Annals of Otology, Rhinology & Laryngology.*"

Jan 1999

Seventh International Symposium on Recent Advances in Otitis Media

June 1-5, 1999

Marriott's Harbor Beach Hotel

Fort Lauderdale, Florida

Hosted by:

Department of Pediatric Otolaryngology Children's Hospital of Pittsburgh & Center for Continuing Education in Health Sciences, University of Pittsburgh School of Medicine

Topics:

Epidemiology
Cell Biology
Biochemistry
Molecular Biology
Immunology
Microbiology
Pathogenesis
Pathology
Screening/Diagnosis
Tubal Function
Prevention
Management
Sequelae
Animal Models

Deadline for submitting abstracts:
December 1, 1998

Sponsored by:

House Ear Institute
International Symposium on Otitis Media, Inc. &
Deafness Research Foundation

SYMPOSIUM DIRECTOR
David J. Lim, M.D.

SYMPOSIUM CO-DIRECTOR
Charles D. Bluestone, M.D.

PROGRAM CHAIR
Margaretha L. Casselbrant, M.D., Ph.D.

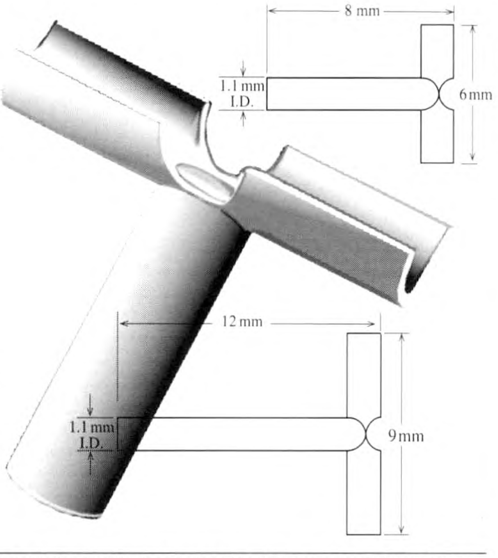
For additional information
Fran Arre
Forbes Travel
Telephone: 412-521-7823
Fax: 412-521-7848
Email: forbes6@mail.sgi.net
www.upmc.edu/ccehs/otitis.htm

Surgeon Controlled™

SuperSoft Silicone™ T-Tubes

*The ideal situation where intubation time is determined by the Otologist, rather than the vagaries of spontaneous extrusion.**

Introduced by Santa Barbara Medco, Inc. The SuperSoft Silicone T-Tube has over 17 years of successful clinical experience as a surgeon controlled ventilation tube. Available in Pretrimmed and Standard sizes.



Advantages of the SuperSoft Silicone T-Tube (SSTT):*

- The surgeon controls the intubation period for the large majority of patients.
- Low spontaneous extrusion rate - less than 10% when flanges are trimmed to 3mm.
- Reported lower residual perforations rate (6.7%) than other long-term ventilation tubes.
- Tube removal can be simply and safely performed in the office because of the shortened SuperSoft Silicone flanges.

Please contact us for additional information and an evaluation sample.

Santa Barbara Medco, Inc.
P.O. Box 6843
Santa Barbara, CA 93160
805/683-1486
FAX 805/683-4864

e-mail: sbmedco@silcom.com or
visit us at our website www.sbmedco.com

*"Lowering the Incidence of Perforation following Goode T-Tube Removal", presented at the American Society of Pediatric Otolaryngology Annual Meeting, May 19, 1990, Toronto, Canada, A.F. Inglis, Jr., M.D., M.A. Richardson, M.D., Taya S. Higgins, R.N. - Children's Hospital & Medical Center, 4800 Sandpoint Way, N.E., P.O. Box C5371, Seattle, WA 98105

Ann Otol Rhinol Laryngol 108:1999

EXPERIMENTAL APPROACHES TO VOCAL FOLD ALTERATION: INTRODUCTION TO THE MINITHYROTOMY

STEVEN D. GRAY, MD
SALT LAKE CITY, UTAH

STEVEN A. BIELAMOWICZ, MD
WASHINGTON, DC

INGO R. TITZE, PHD
IOWA CITY, IOWA

HEATHER DOVE, MA
SALT LAKE CITY, UTAH

CHRISTY LUDLOW, PHD
BETHESDA, MARYLAND

Treatment of challenging laryngeal disorders, such as lamina propria loss or neuromuscular dysfunction, may require novel approaches and techniques. This paper discusses an evolution of experimental techniques for treatment of lamina propria loss and use of the minithyrotomy. These techniques have been used for surgical access for lamina propria substitution, as well as placement of stimulating electrodes. The minithyrotomy is tolerated well by patients, provides access for microscopic instruments with the surgeon's hand close to the tissue of interest, avoids intralaryngeal mucosal incisions, and lines up the direction of dissection in an anterior-to-posterior orientation. This orientation is favorable for particular situations herein discussed. We present anatomic and physiologic concepts relevant to the surgical treatment of lamina propria dysfunction, as well as presenting our clinical experience. This paper is not intended to state how these difficult problems should be handled, but rather, to present our experience in techniques that may prove useful through further development.

KEY WORDS — anatomy, lamina propria, minithyrotomy, scar, thyrotomy, vocal cord, vocal fold.

Obtaining surgical access to the vocal fold structures is challenging. Traditional approaches include a transoral approach, a lateral thyroplasty approach, and a midline laryngofissure approach. We propose a minithyrotomy (MT) as a new approach for surgical manipulation of the vocal fold structures. The MT approach has the advantage of eliminating intralaryngeal mucosal incisions that may lead to scarring of the vocal fold epithelium to the underlying body of the vocal fold. This allows for surgical manipulation of the superficial layer of the lamina propria in a controlled fashion. Instruments can be introduced through the MT in an anterior-to-posterior direction, and visual control is provided by flexible or rigid videoendoscopy. We have developed an MT technique for lamina propria replacement surgery. In addition, MT provides an excellent route for placement of stimulating electrodes for vocal fold closure. The endoscopic view is essential for adequate placement of the stimulating portion of the electrode near the neuromuscular junctions of the thyroarytenoid (TA) and lateral cricoarytenoid (LCA) muscles. Both of these techniques are considered experimental, and we would like the reader to recognize that these procedures are evolving and refinements are expected. In addition, MT can provide access for the placement of an arytenoid adduction suture. A conduit can be placed from anterior to posterior through the TA muscle. The posterior opening of the conduit can be directed to a location immediately lateral to the muscular process of the arytenoid cartilage.

In this paper, we will describe the MT approach and discuss its utility in 3 procedures: a new technique of lamina propria replacement surgery, neuroprosthetic adduction implantation, and a modification of the arytenoid adduction procedure. In the area of lamina propria replacement surgery, this paper will describe the infrafold anatomy, discuss aspects of infrafold configuration relevant to vocal fold oscillation, and relate those topics to possible surgical approaches. For the implantation of a laryngeal electrical stimulator, laryngeal anatomy and stimulator positions will be discussed.

From the Department of Surgery, Division of Otolaryngology, University of Utah School of Medicine, Salt Lake City, Utah (Gray, Dove), the Department of Surgery, Division of Otolaryngology, George Washington University, Washington, DC (Bielamowicz), the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, Iowa (Titze), and the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (NIDCD), Bethesda, Maryland (Ludlow). This work was supported by Public Health Service grant P60 DC00976-07. Dr Ludlow's work was supported by the NIDCD Division of Intramural Research, project Z01 DC 00004-09 and animal protocol 725-95. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of NIH-NIDCD.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, May 9-10, 1998.

CORRESPONDENCE — Steven D. Gray, MD, 50 N Medical Dr, 3C120-SOM, Salt Lake City, UT 84132.

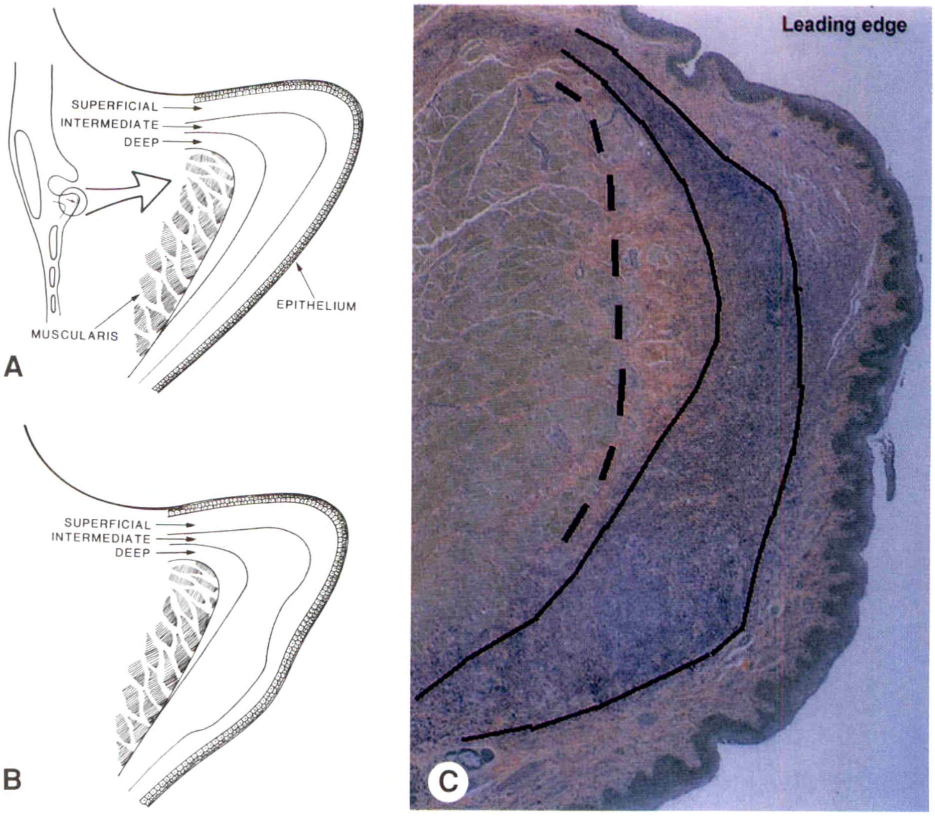


Fig 1. Superficial, intermediate, and deep layers of lamina propria. A) Traditional drawing of lamina propria. B) Another kind of lamina propria that is also frequently seen. Note that intermediate layer creates bulge in vocal ligament in immediate infrafold area. C) Histologic correlate of B is seen from middle-aged man. Vocal ligament is outlined in black, whereas dotted line represents junction of deep layer of lamina propria and vocalis muscle.

LAMINA PROPRIA REPLACEMENT SURGERY

Scarring of the vocal folds is a difficult and challenging clinical disorder. Various options have been proposed for treatment, including speech therapy, collagen injection, medialization laryngoplasty, scar release, and fat implants.[1-5] Although not reported in the literature, other options have been attempted by various phonosurgeons, including mucosal grafts and steroid injections. All of these procedures may have a role in treating scarred vocal folds, depending on the severity and extent of the scarring. In this paper, only treatment of lamina propria loss or dysfunction by replacement or reconstruction techniques will be discussed.

It has long been recognized that the start of the mucosal wave occurs in the infrafold region. Mucosal "bunching" or "upheaval" begins approximately 3 mm below the leading edge of the vocal folds, at the level of the inferior portion of the TA muscle.[6,7] The exact beginning location of the mucosal wave varies, since it is partially dependent on amplitude of vibration, frequency of vibration, and glottic configuration. Regardless of the precise location, normal vocal production depends on the free movement of the infraglottic vocal fold mucosa. Any impairment of the lamina propria in this region will result in vocal dysfunction. Ideally, this tissue movement should occur easily, with little energy required, allowing for mucosal movement in the vertical plane. When the vocal fold and especially the infrafold tissue have been injured or destroyed, the location of mucosal wave initiation is altered.[5] It is likely that some of our attempts to improve vocal fold scar have fallen short due to failure to adequately address and correct the infrafold region.

When considering aspects of lamina propria reconstruction, it is helpful to examine the normal infrafold anatomy. The vocal fold anatomy has been described in detail in many elegant articles.[8,9] Typically, the lamina propria layers are drawn schematically, and the superficial and intermediate layers are shown to be the thickest at the leading edge of the vocal folds, with a gradual tapering of the layers as they proceed inferiorly. Histologic examination of human larynges demonstrates considerable variation in the tapering of the lamina propria layers in the infrafold region. Specifically, the intermediate layer of the lamina propria may remain quite thick and wide in the infrafold area and on occasion may bulge in the infrafold area, due to thickness of the extracellular matrix components. This is best illustrated in Fig 1A,B.

Figure 1C shows that the intermediate layer (outlined) may be almost as thick in the infrafold region as the leading edge. The intermediate layer is composed of elastin fibers, hyaluronic acid, and fibromodulin.[10,11] These molecules give the tissue qualities of elasticity and viscosity appropriate for tissue oscillation. The effect of this infrafold bulge is un-

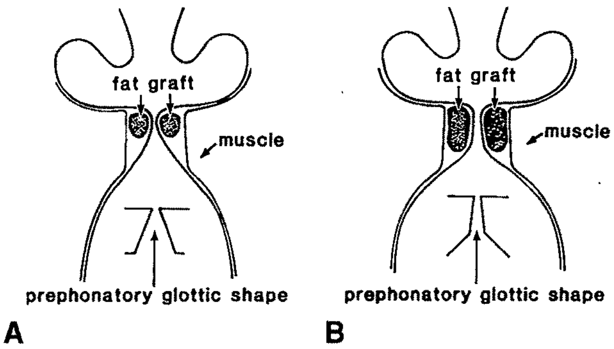


Fig 2. Illustration of effect position of any implant to lamina propria has on glottic configuration. Size of implants is exaggerated for illustrative purposes. A) Demonstrates injected, implanted substance only at leading edge of vocal fold and consequent convergent phonatory shape of glottis (not good shape for oscillation of tissue). B) Demonstrates effect of substance extending more infrafold to provide better phonatory glottic shape conducive to tissue oscillation.

der investigation, but it is conceivable that this bulge biomechanically facilitates mucosal wave upheaval, vibrational amplitude, and vertical travel. Not all larynges have this infrafold thickness of the intermediate layer, and there are infrafold differences from anterior to posterior along the membranous fold. Anteriorly, the tapered layers shown in Fig 1A are seen; more posteriorly in the membranous fold, infrafold intermediate layer thickening occurs.

The shape of the infraglottis is also important. If only the free edge of the vocal fold is augmented and the infrafold portion is neglected, the parameters needed for tissue oscillation may actually become worse (Fig 2).

The oscillation threshold pressure (Pth) can be determined by using the following equation for a glottal shape, as shown schematically in Fig 2.[16]

$$P_{th} = (2/T)(Bc)\frac{X_1^2}{X_1 + X_2}$$

In this equation, X_1 is the glottal width at the bottom and X_2 is the glottal width at the top, T is the vocal fold thickness, B is a viscous damping coefficient in the tissue, and c is the mucosal wave velocity. Note that P_{th} increases as X_1 increases, indicating that the "ease of phonation" is reduced by a large separation of the vocal folds at the bottom (a large convergence). The best case is a rectangular glottis, shown in Fig 2B, where $X_1 = X_2$, for which case the threshold pressure becomes

$$P_{th} = (1/T)(Bc)(X_1)$$

Note that P_{th} is lowered by decreasing the glottal width X_1 (better adduction), increasing the vocal fold thickness (T), lowering the viscous damping (B), and lowering the mucosal wave velocity (c).

The relevance to the repair or replacement of injured lamina propria is that restoration of the infrafold region is critical and should be addressed in surgical reconstruction of vocal fold function if we are to be successful. The infrafold region may often be neglected in our evaluation of the scarred fold because of the difficulty examining this region with traditional clinical techniques. With stroboscopy, the infrafold region is usually obscured by the leading, more medial, edge of the vocal fold. Often, the only indication that severe dysfunction is present is that no mucosal wave can be seen traveling up from the infrafold region.[5,12] Another option to verify the extent of scarred vocal folds is to perform the microlaryngeal infusion technique described by Kass et al.[13] Normal vocal folds infuse easily and symmetrically, whereas scarred vocal folds do not. They will show asymmetries and areas of restriction upon infusion.

Tissue Properties. When the lamina propria has been injured, lost, or scarred, freedom of tissue motion is impaired. If the tissue has reduced and restricted motion, it becomes stiff and unable to oscillate.

One of the properties affecting freedom of motion is viscoelasticity. As has been described, the extracellular matrix is a composition of proteins consisting of elastins, collagens, proteoglycans, glycoproteins, carbohydrates, and lipids. Particularly, some of the proteoglycans affect the viscosity of the tissue.[14,15] Viscosity determines the amount of energy required for tissue oscillation. As tissue viscosity increases, the amount of energy required to overcome frictional forces for tissue oscillation increases.[16] This is manifested in the parameter B in the equations above. With injured or scarred lamina propria, the normal beneficial proteins such as hyaluronic acid and elastin material are replaced by protein components such as collagen fibers and fibronectin, which result in increased tissue viscosity.

To correct lamina propria loss or scarring, one should consider procedures that restore freedom of motion and lower tissue viscosity. While future studies may identify a more ideal injectable material, such as hyaluronic acid, we are currently investigating the use of a fat graft to improve both freedom of motion and tissue viscosity. The construction of a cellular layer such as fat may help in maintaining freedom of tissue motion. With the creation of this cellular layer between the cover (epithelium and superficial layer) and body (deep layer and TA muscle), the fat cells may prevent fibroblast migration and resultant scarring between the two layers. The concept of surgically freeing up the scarred area is not new.[17] Unfortunately, without some mechanism to prevent fi-

TABLE 1. RESULTS OF KENALOG INJECTIONS TO VOCAL FOLD SCAR

	Patient 1		*Patient 2*		*Patient 3*	
Measures	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Mean jitter (%)	2.9	0.2	0.8	0.4	1.2	0.7
Mean SNR (dB)	13	27	20	29	22	22
Mean DC flow (mL/s)	729	672	274	202	373	254
Mean MPT (s)	6	5	11	13	7	4
Mean AC:DC ratio	0.85	0.51	0.79	1.17	0.40	0.76
Mean habitual subglottic pressure (cm H2O)	13.7	9.6	8.4	5.4	13.3	9.8
Perceptual rating*	5	1-2	2-3	2	3	3-4

Operations were performed in 1990 to 1994. Recordings performed at least 6 months postoperatively.

SNR — signal-to-noise ratio, MPT — maximum phonation time.

*Performed by speech pathologists (not blinded) on 7-point scale (1 = normal, 7 = aphonic).

broblast migration and new scar in the surgically injured site, one would expect a short-term surgical result. Perhaps placing a layer of fat between the body and cover of the vocal fold would maintain a separation of the two layers.

Another reason to choose fat is that Chan and Titze[18] showed fat has viscous properties similar to those of normal human lamina propria. Normal human lamina propria has a dynamic viscosity of about 3 to 4 pascal-second (Pa-s) at 10 Hz, while fat is about 4 Pa-s. Of interest is that a proteoglycan mixture such as hyaluronic acid is around 1 to 2 Pa-s, whereas collagen mixtures are about 10 Pa-s. Low values are less viscous (like water), while high values are more viscous (like glue). Viscosity has a linear relationship with the effort required to oscillate human vocal folds.[16] Tissue with higher viscosity will require more effort. For these reasons, fat was chosen as a possible substance for lamina propria replacement.

Surgical Approaches. We have used a transoral microlaryngoscopic approach to the scarred fold, with scar release and/or steroid injection, or insertion of a fat graft stabilized with 7-0 or 6-0 microsutures. Although our early results were often favorable with these techniques, within 6 months the patients began to lose the benefits of the surgery. Table 1 gives clinical examples of Kenalog injections.

Notice from Table 1 that the results are quite variable. Although jitter improved in all, some of the aerodynamic measures became worse. Most important, the perceptual rating did not change in 2 of the 3 patients.

It is easier to understand the relapse associated with simple scar release followed by steroid injection, since scar formation is probably recurring. It is more difficult to understand the relapse associated with transoral fat implantation through a superior cordotomy. It appears that when fat is implanted transorally, it tends to migrate superiorly in the cordotomy incision. This migration results in the fat's being in the suprafold area and also creates a convergent glottic shape, which, as discussed earlier, may be detrimental to Pth.

We then employed a laryngofissure approach described by Wexler et al[19] in a study of fat grafts to the scarred vocal folds of dogs. In this study, a laryngofissure approach was chosen because creating a tunnel pocket for fat implantation required microscopic dissection with ear instruments. Lifting the epithelium off the TA muscle in a continuous pocket without any epithelial tears required microscopic control of the instruments and careful tissue handling. Additionally, the ideal pocket location was primarily in the infrafold region without a significant suprafold component. A suprafold component allows implanted fat to migrate superiorly in the pocket, since airflow and phonation tend to propel tissue upward. The final location of the implanted fat is critical, since this affects prephonatory glottic configuration. When this technique is performed, the implanted fat is clearly visible through the epithelium and casts an evident yellow hue to the vocal fold. If a yellow hue is not seen, the fat may have been placed too deep. If the fat is placed too deep, the viscous properties that fat may convey for vocal fold oscillation are not located superficially enough to assist tissue movement, and restricted tissue movement persists (Fig 3).

The laryngofissure approach appeared to satisfy the goals of the fat implantation. A pocket 3 to 4 mm in vertical height along the entire membranous fold and infrafold area could be packed relatively tightly with fat through an incision that could be closed to prevent fat extrusion.[12] The results from the Wexler et al[19] and the Jiang et al[20] studies were very acceptable.

We pursued fat implantation in humans on the basis of these results, optimistic of obtaining similar functional improvement in patients with scarred vo-

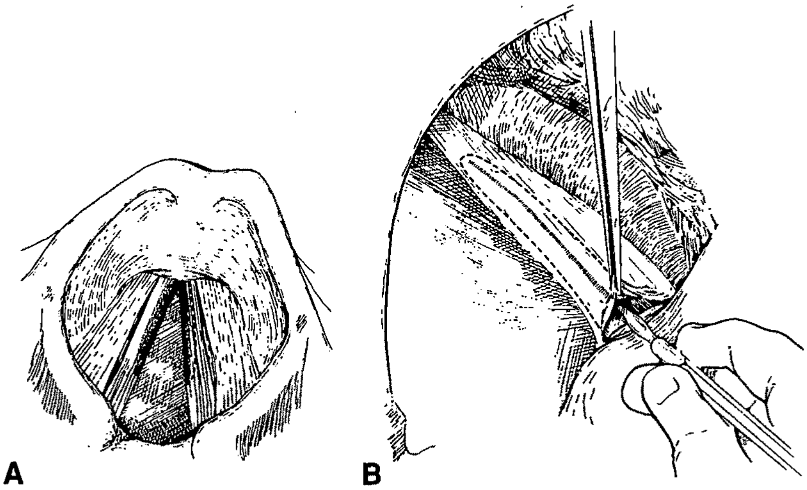


Fig 3. Sketches of laryngofissure approach. A) Stippled area represents scarred lamina propria. B) Ear instruments are used to free up scarred cover from underlying muscle. Pocket is packed with fat in symmetric fashion. Pocket is created so that infrafold area is included in pocket, whereas suprafold area is not dissected.

cal folds.

METHODOLOGY AND RESULTS

Laryngofissure–Lamina Propria Surgery. Using a laryngofissure approach (described above), we performed fat implantation to scarred lamina propria in 3 cases (Tables 2 and 3). We wanted to make sure that a relatively long follow-up had occurred, as fat may absorb and scarring changes may take place up to 2 years later.

In retrospect, we believe that in our first case we should have made the pocket slightly larger and grafted more fat due to anticipated fat resorption. The fat was resorbed more in these human patients than in the dogs. However, the resorption was less than we experienced with fat injections. With each procedure, we learned to place more fat and to create a more generous pocket without extending the superior aspect of the fold. No further surgery has been performed on the second and third patients. The first patient moved to Wisconsin after 18 months postoperatively and had some voice deterioration. She has had 2 additional fat injections into the created fat layer by Dr James Brandenburg (University of Wisconsin). Both injections have further improved her voice.

Minithyrotomy–Lamina Propria Surgery. Although the patients have all been happy with their voice quality, we were not satisfied with the need for a laryngofissure to provide exposure. From the above results, we concluded that fat implantation to the infrafold area and leading edge of the fold was a clinically useful procedure if it could be performed without a laryngofissure. An MT as an entrance site for the instruments to be used with an endoscope or microscope in the larynx for visualization was considered. This approach is not unlike other minimally invasive endoscopic operations in which visualization and instrument access are obtained from different sites. The MT is created by cutting or drilling about a 4-mm window in the thyroid cartilage slightly off the midline of the anterior commissure area through a 1- to 2-cm anterior neck incision. The site of the MT is determined by placing a needle through the thyroid cartilage at the site at which instruments will be placed directly horizontal to the vocal fold edge. Ideally, the needle should enter the vocal fold just deep to the epithelium at the free edge of the vocal fold or slightly infrafold. By slightly moving the needle, the position of the needle can be determined by viewing the tissue movement videoendoscopically.

The direction of dissection must be horizontal to the fold so that a straight pocket or tunnel can be created. If the direction is not horizontal, the pocket will be larger anteriorly and smaller posteriorly, and the fat graft will bunch anteriorly. Once the MT is

TABLE 2. PATIENT INFORMATION FOR FAT IMPLANTATION

Pt No.	*Age*	*Sex*	*Date of Surgery*	*Clinical Data*
1	37	F	1990	Vocal fold entire length stripping (by operative report) twice for nodular thickening 5 and 4 years prior to 1990. No mucosal wave was present.
2	66	F	1992	Benign neurological tumor resulting in unilateral paralysis treated with Teflon 10 years earlier. Recurrent, large Teflon granulomas treated with many carbon dioxide laser excisions over 6 years. Eventually had severe unilateral scarring of fold.
3	42	M	1994	Anterior half of vocal fold removed (partial cordectomy) due to benign tumor. Had aspiration, severe dysphonia, and scarring of remaining fold remnant.

TABLE 3. RESULTS FROM FAT IMPLANTATION

Measures	*Patient 1*		*Patient 2*		*Patient 3*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Mean jitter (%)	UM	0.41	2.62	0.4	1.3	0.51
Mean SNR (dB)	UM	18.4	12.25	21.8	17.7	27.8
Mean MPT (s)	9	14	3	5	10	10*
Mean DC flow (mL/s)			409	275	340	418*
Mean AC:DC ratio			0.34	0.62	0.87	1.36
Mean habitual subglottic pressure (cm H2O)			15.53	8.8	7.65	5.69
Perceptual rating†	5	2	5	4	3-4	1

UM — unmeasurable (signal was too nonperiodic for software C-Speech to track for measurements). Open cells indicate that tests were not performed. (In 1990, aerodynamic measures were not obtained preoperatively.)

*Patient 3 showed continued improvement in acoustic measurements for 2 years. Aerodynamic measurements improved postoperatively and then, at about 13 months, worsened to values reported. Earlier, 9-month values included 267 mL/s for flow and 13 seconds for MPT.

†Performed by speech pathologists (not blinded) on 7-point scale (1 = normal, 7 = aphonic).

created, then a straight pick (used in ear surgery) is placed to first create a small tunnel just under the epithelium from the anterior commissure to the vocal process. Then the needle is used again to create a second pass and then a third. Multiple passes are made until the needle can be easily passed from the anterior commissure to the vocal process in the infrafold and leading edge areas. This technique can be easily monitored and visualized with a microscope or a 70° telescope. Current suspension devices make this somewhat awkward, but we place a sticky sterile plastic wrap around our suspension device to maintain sterility (Fig 4[19]).

After the small tunnels have been created, they are connected into a single pocket with ear knives (like a Tabb) or scissors, and the small fat pieces (obtained from the neck) are placed. A sharp dissection without a plane of dissection may result in accidental tearing or cutting through the epithelium and allow fat extrusion and bacterial contamination. Both are possible causes of fat resorption. The pocket should include the area of scar, the free edge, and 2 to 3 mm inferior to the scar. The fat graft should be placed so as to maintain some consistency in the density of the fat across the pocket. The fat graft should be symmetrically distributed across the vocal fold. Lumpy fat grafts will not impart symmetry.

We performed an MT on an 84-year-old man with severe bowing, sulcus vergeture, and bilateral Teflon granulomas. He was treated with bilateral Teflon in-

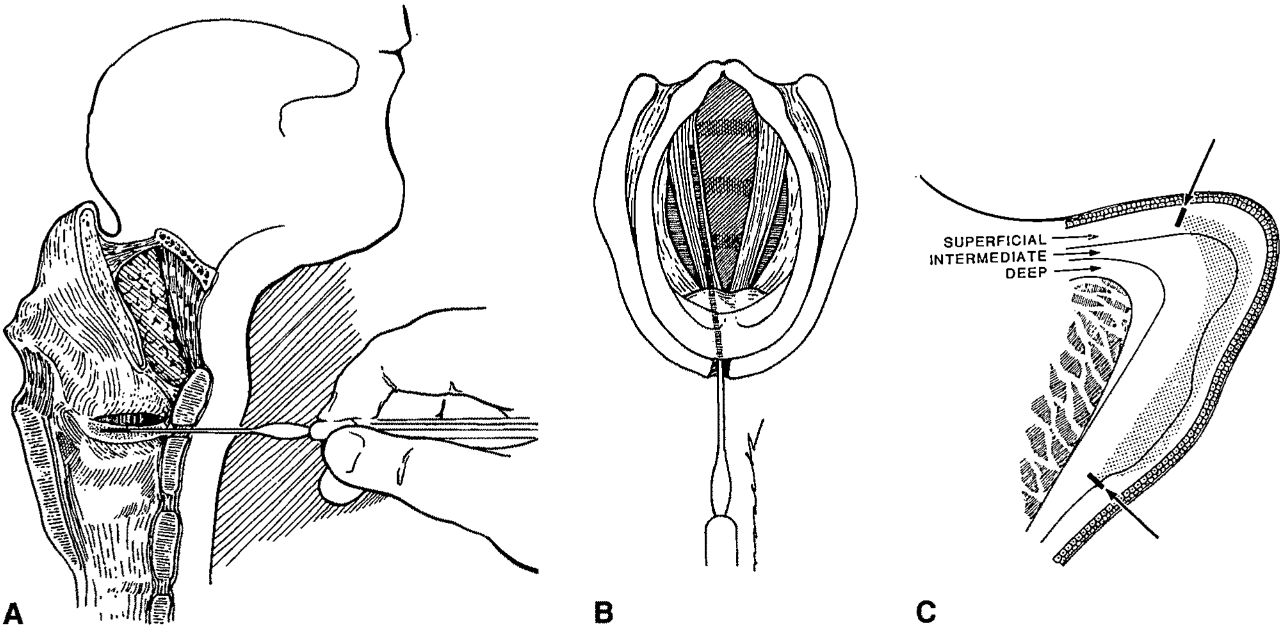


Fig 4. Three illustrations showing minithyrotomy discussed. A,B) Small bur hole or window is created through thyroid cartilage. Instruments are then placed through this thyroid cartilage to infrafold edge of vocal fold. C) Stippled area shows location of pocket created. Black bars are placed to indicate limits of pocket as based on Wexler et al[19] study and on our patient experience.

TABLE 4. MINITHYROTOMY PATIENT DATA

	Dec 11, 1996	*Jan 7, 1997*	*Dec 18, 1997*	*Normal Range*
Mean jitter (%)	2.03	1.16	0.64	≤0.3
Mean shimmer (%)	10.04	7.82	1.88	≤2
Mean SNR (dB)	22.35	21.6	28.37	≥30
MPT (s)	10	11	10	15-20

jections twice, a few years earlier, for severe bowing that did not improve his voice. In our evaluation he had hard, firm vocal folds with no mucosal waves and was also recognized as having bilateral large sulcus vergeture. We removed the Teflon from the folds through a lateral thyroplasty approach (introduced to the technique by Dr James Netterville, Vanderbilt University); however, the sulcus vergeture and scarring of the lamina propria from the Teflon persisted. An MT was performed in June 1996. The procedure took a little less than 2 hours and the patient has been happy with the result. So far, his acoustic perturbation values are better postoperatively and have even improved with time. His aerodynamic data are only slightly improved, and have not deteriorated over the last $1^1/2$ years (Table 4). Although his voice is not normal, he has been happy with the results of the surgery.

At this point in our clinical research, we express satisfaction with the MT approach, but not with the currently available instruments for this operation. We need finer instruments that allow dissection of the epithelium from the underlying tissue. The ear instruments that were relatively adequate for a laryngofissure approach did not work as well for the endoscopic technique. It was relatively easy to create the tunnels between the scarred epithelium and the underlying tissue and muscle, but it was difficult to connect the tunnels into a single, relatively symmetric pocket with the ear knives and scissors. The scissors were too big to fit in the pocket, and the knives were not completely adequate in taking down the fibrous adhesions separating the tunnels. Smaller scissors to cut the adhesions would be an improvement. Sharp, fine microknives that cut from side to side would also help.

MINITHYROTOMY PLACEMENT OF STIMULATING ELECTRODES

Stimulation of the adductor muscles in the larynx is currently being investigated. Dynamic adduction of the vocal folds could possibly assist in the management of patients with dysphagia and aspiration due to central nervous system dysfunction and brain stem injury including stroke and amyotrophic lateral sclerosis.

We have currently implanted 12 dogs with a prototype of a functional electrical stimulation unit for dynamic vocal fold closure. We have independently devised an MT procedure for the implantation of electrodes into the larynx. Our goal has been functional neuromuscular stimulation of the TA and LCA muscles. The larynx has been implanted in 2 different routines. Some animal larynges have been implanted with a ventricular fold and a true vocal fold electrode bilaterally. The goal of this implantation within 2 portions of the TA muscle was to mimic true and false vocal fold closure that is seen with a normal swallow. Other animals have been implanted with electrode combinations that include the LCA muscle. We have noted that arytenoid closure occurs best with stimulation of the lateral aspect of the body of the arytenoid cartilage.

Our approach to implantation of the electrodes for functional electrical stimulation has employed an MT approach with videoendoscopic guidance similar to the approach for fat grafting of the vocal folds. In this approach, the anterior larynx is exposed and the location of the anterior commissure is confirmed by placing a 22-gauge, 1.5-cm hypodermic needle through the thyroid cartilage. For the true vocal fold TA electrode, the needle is inserted approximately 3 to 4 mm off midline and half the distance between the superior border of the cricoid cartilage and the thyroid notch. The needle is inserted in a 15° lateral direction and horizontally within the inferior TA muscle. Placement of the needle in this location is confirmed by videoendoscopy. The depth of insertion is determined by manual motion of the arytenoid cartilage while guiding the needle tip in a medial direction. A 3-mm cutting bur is then used to open the MT at the exact insertion site of the hypodermic needle. The MT bur hole is angled to accommodate the direction of insertion. Great care should be taken in creating the MT to prevent communication with the airway. After creating the MT, a 1-gauge needle loaded with the stimulating electrode is passed in a fashion similar to that of the hypodermic needle under videolaryngoscopic guidance. The carrier needle is removed and the stimulating electrode remains adjacent to the arytenoid cartilage body. The electrode exits through the MT and is connected to an implantable stimulating device.

The placement of the superior TA electrode within the ventricular fold occurs in a similar fashion. The hypodermic needle is placed through the thyroid cartilage at the midpoint of the superior and inferior borders and 3 to 4 mm lateral to midline. The needle is directed 15° laterally and 15° superiorly. Visual confirmation within the ventricular fold is made by videolaryngoscopy. Again, a 3-mm cutting bur is used to make the MT, and the carrier needle and electrode are inserted in a fashion similar to that of the hypodermic needle.

While certain adaptations will be required in humans, the basic concept of the MT will likely persist. In the dog, we have had no difficulty with edema or hematoma formation within the larynx, despite placing stimulating electrodes in both true and false vocal folds bilaterally.

MINITHYROTOMY–ARYTENOID ADDUCTION

In addition, we have found the MT to be useful in placing an arytenoid adduction suture. This is currently our preferred initial operation for patients with a vocal fold paralysis with a lateralized arytenoid cartilage. We reviewed our experience with primary arytenoid adductions performed for vagal paralysis after skull base surgery at George Washington University and found that 16 of 20 patients had complete glottic closure on videostroboscopy with excellent voice results. The remaining patients were noted to have a persistent anterior glottal gap requiring a thyroplasty as a secondary procedure. All arytenoid adductions were performed under general anesthesia immediately after skull base surgery.

Our current arytenoid adduction procedure is a modification of the procedure performed by Berke.[21] Initially, the midline of the thyroid cartilage is skeletonized, as well as the posterior larynx. The muscular attachments of the thyrohyoid and inferior constrictor muscles are taken down. The external branch of the superior laryngeal nerve is routinely identified and preserved. The pyriform mucosa is elevated posteriorly from the undersurface of the thyroid cartilage. The muscular process is identified without disturbing the fascial insertion of the posterior cricoarytenoid and LCA muscles. The cricoarytenoid joint is not opened. A 4-0 Prolene suture is placed through the fascial covering of the muscular process of the arytenoid. An MT is created with a 3-mm cutting bur as near to the anterior midline as possible and as close to the inferior border of the thyroid cartilage as possible without jeopardizing the integrity of the inferior border of the thyroid cartilage. Superficially, the MT is angled toward the opposite side. A 16-gauge angiocath needle is passed from the MT to the lateral aspect of the body of the arytenoid cartilage with minimal force and trauma. The Prolene suture is passed from posterior to anterior through the angiocath needle acting as a conduit. The angiocath is withdrawn and the suture is tied over a 4-hole microplate.

CONCLUSION

This paper is not an attempt to state how these difficult problems in the larynx should be handled. It is merely a report on our experimental approaches to these problems. We have found that using an MT can give a unique approach to the larynx. It is well tolerated and minimally invasive. Visualization can be obtained transorally with a video camera on an endoscope. Instrument access is excellent; however, refinements in the surgical instruments are necessary. For lamina propria replacement surgery, implantation of stimulating electrodes, and the placement of the arytenoid adduction suture, an MT approach gives a favorable direction and approach to accomplish the goals of the surgery. The MT is versatile in that it can provide access to the infrafold and leading edge areas for lamina propria surgery, or to the LCA and TA muscles for electrode placement.

The results from the laryngofissure and MT approaches to the scarred lamina propria suggest that one may operate on the lamina propria and expect voice improvement. In our small experience of medium-length follow-up, we have been pleased and encouraged, but certainly not satisfied, with our patient outcomes. They have not been as successful as those of the canine research. As with all surgeries, there is a learning curve, and we continue to make modifications. We expect many more modifications by ourselves and others who are performing this type of work. The correct size of the pocket, the amount of fat (or other material) placed, and creating symmetry are all areas that need further work. Perhaps better substances will become available to improve tissue viscosity. Regardless of these potential changes in the future, we are starting to feel more comfortable and satisfied with the surgical approaches.

REFERENCES

1. Woo P, Casper J, Colton R, Brewer D. Diagnosis and treatment of persistent dysphonia after laryngeal surgery: a retrospective analysis of 62 patients. Laryngoscope 1994;104: 1084-91.

2. Ford CN, Bless DM, Loftus JM. Role of injectable collagen in the treatment of glottic insufficiency: a study of 119 patients. Ann Otol Rhinol Laryngol 1992;101:237-47.

3. Ford CN, Bless DM. Collagen injection in the scarred vocal fold. J Voice 1987;1:116-8.

4. Koufman JA, Isaacson G. Laryngoplastic phonosurgery. Otolaryngol Clin North Am 1991;24:1151-71.

5. Benninger MS, Alessi D, Archer S, et al. Vocal fold scarring: current concepts and management. Otolaryngol Head Neck Surg 1996;115:474-82.

6. Matsushita H. The vibratory mode of the vocal folds in the excised larynx. Folia Phoniatr (Basel) 1975;27:7-18.

7. Baer T. Investigation of phonation using excised larynx [Thesis]. Cambridge, Mass: Massachusetts Institute of Tech-

nology, 1975.

8. Hirano M. Structure of the vocal fold in normal and disease states. Anatomical and physical study. ASHA 1981;11:11-30.

9. Gray SD, Hirano M, Sato K. Molecular and cellular structure of vocal fold tissue. In: Titze IR, ed. Vocal fold physiology: frontiers of basic science. 1st ed. San Diego, Calif: Singular Publishing, 1993:1-34.

10. Hammond T, Zhou R, Hammond E, Pawlak A, Gray SD. The intermediate layer: a morphologic study of the elastin and hyaluronic acid constituents of normal human vocal folds. J Voice 1997;11:59-66.

11. Pawlak AS, Hammond T, Hammond E, Gray SD. Immunocytochemical study of proteoglycans in vocal folds. Ann Otol Rhinol Laryngol 1996;105:6-11.

12. Okamura H, Yumoto E, Okamoto K. Wound healing of canine vocal folds after phonosurgery. Ann Otol Rhinol Laryngol 1987;96:425-8.

13. Kass ES, Hillman RE, Zeitels SM. Vocal fold submucosal infusion technique in phonomicrosurgery. Ann Otol Rhinol Laryngol 1996;105:341-7.

14. Balazs EA, Gibbs DA. The rheological properties and biological function of hyaluronic acid. In: Balazs EA, ed. Chemistry and molecular biology of the intercellular matrix. Vol 3. New York, NY: Academic Press, 1970:1241-53.

15. Zhu WB, Mow VC. Viscometric properties of proteoglycan solutions at physiological concentrations. In: Mow VC, Ratcliffe A, Woo S, eds. Biomechanics of diarthrodial joints. New York, NY: Springer-Verlag, 1990:313-44.

16. Titze IR. The physics of small-amplitude oscillation of the vocal folds. J Acoust Soc Am 1988;83:1536-52.

17. Bastian RW. Benign mucosal and saccular disorders: benign laryngeal tumors. In: Cummings CW, ed. Otolaryngology–head and neck surgery. 2nd ed. St Louis, Mo: Mosby–Year Book, 1992:1897-924.

18. Chan RW, Titze IR. Viscosities of injectable biomaterials in vocal fold augmentation surgery. Laryngoscope 1998;108: 725-31.

19. Wexler DB, Jiang J, Gray SD, Titze IR. Phonosurgical studies: fat-graft reconstruction of injured canine vocal cords. Ann Otol Rhinol Laryngol 1989;98:668-73.

20. Jiang JJ, Titze IR, Wexler DB, Gray SD. Fundamental frequency and amplitude perturbation in reconstructed canine vocal folds. Ann Otol Rhinol Laryngol 1994;103:145-8.

21. Berke GS. Voice disorders and phonosurgery. In: Bailey BJ, ed. Head and neck surgery–otolaryngology. Philadelphia, Pa: WB Saunders, 1993:644-57.

≈

ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY 1999 MIDWINTER RESEARCH MEETING

The Association for Research in Otolaryngology 1999 MidWinter Research Meeting will be held February 14-18, 1999, in St Petersburg Beach, Florida. For information, contact ARO Meetings Department, 19 Mantua Rd, Mt Royal, NJ 08061; telephone (609) 423-7222 ext. 350; fax (609) 423-3420; e-mail meetings@aro.org; web site http://www.aro.org.

Ann Otol Rhinol Laryngol 108:1999

ECTASIAS AND VARICES OF THE VOCAL FOLD: CLEARING THE STRIKING ZONE

ILAN HOCHMAN, MD
TEL AVIV, ISRAEL
ROBERT E. HILLMAN, PHD
BOSTON, MASSACHUSETTS
ROBERT T. SATALOFF, MD, DMA
PHILADELPHIA, PENNSYLVANIA
STEVEN M. ZEITELS, MD
BOSTON, MASSACHUSETTS

Vascular malformations such as ectasias and varices (Es and Vs) are frequently encountered in patients who present with recurrent vocal fold hemorrhage and/or other traumatic vocal fold lesions. This study examined Es and Vs with regard to their anatomic presentation, phonomicrosurgical management, and treatment outcome. Forty-two patients (39 of them singers) were treated for a total of 87 Es and Vs: 67 of 87 (77%) were on the superior surface of the vocal fold and 20 of 87 (23%) were on the medial surface of the vocal fold. Eighty-three percent were located in the middle musculomembranous region (the striking zone), where the greatest aerodynamically induced shearing stresses occur during phonation. Treatment was performed with carbon dioxide laser cauterization (13 patients), or a new technique utilizing cold instrument excision by means of epithelial cordotomies (23 patients), while a combined approach was employed in 6 patients. Comparisons of preoperative and postoperative stroboscopy revealed improvement or no significant change in all patients in whom the cold instrument technique was used, and increased epithelial stiffness was noted in 4 of 19 patients in whom the carbon dioxide laser was used. Clearing the striking zone appears to have halted further hemorrhages by removing the the fragile Es and Vs from this injury-prone region of the vocal fold. Interpretations of stroboscopic examinations were directed at providing new insights into the biomechanical forces of vocal fold vibration that probably contribute to the genesis of Es and Vs in the vocal folds.

KEY WORDS — ectasia, microlaryngoscopy, phonomicrosurgery, phonosurgery, varices, vocal bleed, vocal cord, vocal fold, vocal hemorrhage.

INTRODUCTION

Vocal fold hemorrhage was observed in a pregnant woman in 1873 by Fraenkel.[1] At the first meeting of the American Laryngological Association, in 1879, Hartmann[2] first reported an acute vocal fold hemorrhage in a performing artist. A decade later, Porter[3] described his experience with acute vocal fold hemorrhages in singers and other vocal overusers. In that work, he explained that hemoptysis should not be automatically diagnosed as pulmonary tuberculosis and that a laryngoscopy is mandatory to identify the site of bleeding. Local application of chemical caustics or electric cautery to halt recurrent vocal fold hemorrhage was common practice from the beginning of laryngology.[4] A century later, Baker[5] reported the first series of patients with recurrent submucosal vocal fold hemorrhage. In this seminal contribution, he described the typical superior-surface location of traumatically induced subepithelial vascular malformations. Further, he established that direct laryngoscopic excision of these lesions was the optimal approach to prevent future hemorrhages.[5]

There is little discussion in the literature regarding the nomenclature for subepithelial vascular malformations, which are commonly referred to as ectasias and varices (Es and Vs). Varix is a Latin term and is defined as a dilated vein, while ectasia is a Greek term and is defined as a dilated tubular structure.[6] Due to the lack of well-accepted terminology, we adopted the following terms for convention: 1) varix (Figs 1A, 2A, and 3); 2) papillary ectasia (Figs 1A and 2A); and 3) spider telangiectasia (Fig 2A).

Our clinical observations have generally revealed 3 visual patterns of vascular malformations for which we have utilized the term Es and Vs. In this work, varices will be defined as enlarged veins or acutely tortuous vessels. Papillary ectasias resemble spheroid-appearing coalescent hemangiomas. Spider telangiectasias resemble the dermatologic disorder and demonstrate a fine network of inappropriately oriented vessels. We did not stratify these entities herein, due to the retrospective nature of the investigation, the frequent difficulty in segregating the lesions since many have multiple characteristics, and the difficulty

---

From the Department of Otology and Laryngology, Harvard Medical School (Hochman, Hillman, Zeitels), and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary (Hochman, Hillman, Zeitels), Boston, Massachusetts, and the Department of Otolaryngology, Thomas Jefferson University, and the Department of Otolaryngology, Allegheny University Hospitals, Philadelphia, Pennsylvania (Sataloff). Dr Hochman is currently in the Department of Otolaryngology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. This research was supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant R01-DC0026.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, May 9-10, 1998.

CORRESPONDENCE — Steven M. Zeitels, MD, Dept of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

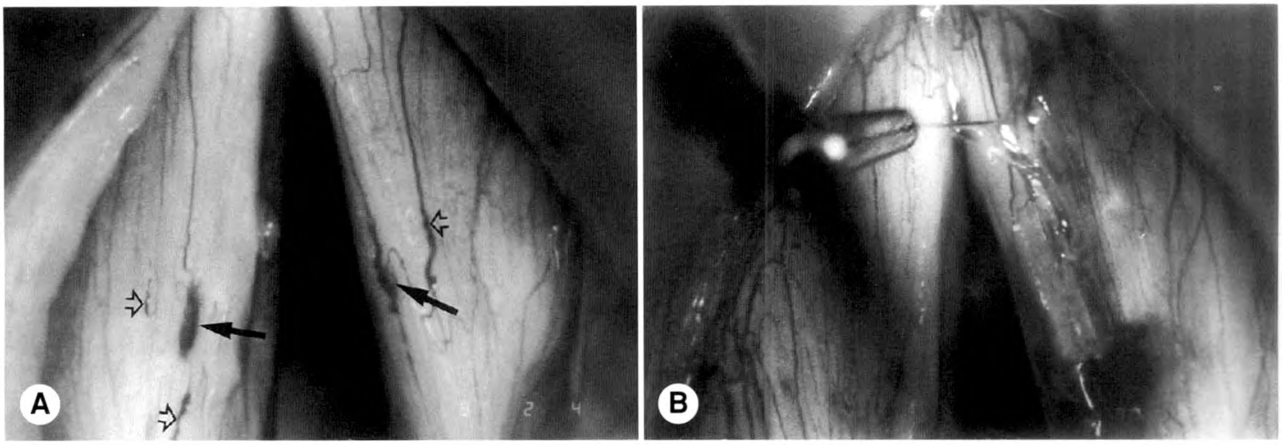


Fig 1. Classical vocalist with history of recurrent hemorrhage. A) Multiple varices (open arrows) and ectasias (solid arrows) are noted in striking zone. Only some of lesions required excision. B) Cold dissection has been utilized to resect aberrant microvasculature. Pediatric forceps are used to extract varix from its subepithelial position in superficial lamina propria. There is minimal disturbance of normal superficial lamina propria.

in maintaining the same level of scrutiny in the visual analysis of the lesions. This is well demonstrated by Figs 1A and 2A.

Ectasias and varices have been associated with vocal abuse, as have other benign vocal fold lesions such as nodules and polyps,[7-9] and are most frequently encountered in female vocalists.[5,7,10-12] With respect to the underlying microvascular anatomy of the larynx, standard histopathologic and electron microscopic analysis of the microvascular anatomy of the larynx reveals that the blood vessels in the superficial lamina propria (SLP) course in a longitudinal direction with frequent arteriovenous anastomoses.[13] This vascular pattern is believed to facilitate continuous blood flow through the microcirculatory system of the SLP during high-pressure phonation. Therefore, vessel patency is maintained despite the aerodynamically induced shearing stresses that are placed on the microvasculature in the SLP during vocal fold oscillation.

Nakai et al[13] reported an absence of direct communication between the microvasculature of the SLP and the vocalis muscle, which allows for maximal flexibility of the mucosal cover over the ligamentous and muscular body of the vocal fold. Franz and Aharinejad[14] believe that there are venous communications between the mucosa and the muscle layer. However, high-magnification (40×) intraoperative examination of the SLP supports the observations of Nakai et al. Franz and Aharinejad[14] correctly proposed that the undulating course of the subepithelial vessels accommodates to extreme changes in the length and viscoelastic tension of the vocal folds' layered microstructure without compromising its blood supply.

Analysis of the ultrastructure of the endothelial cells of the SLP demonstrates intermediate-thickness filaments that exist near the cell nucleus and bund-

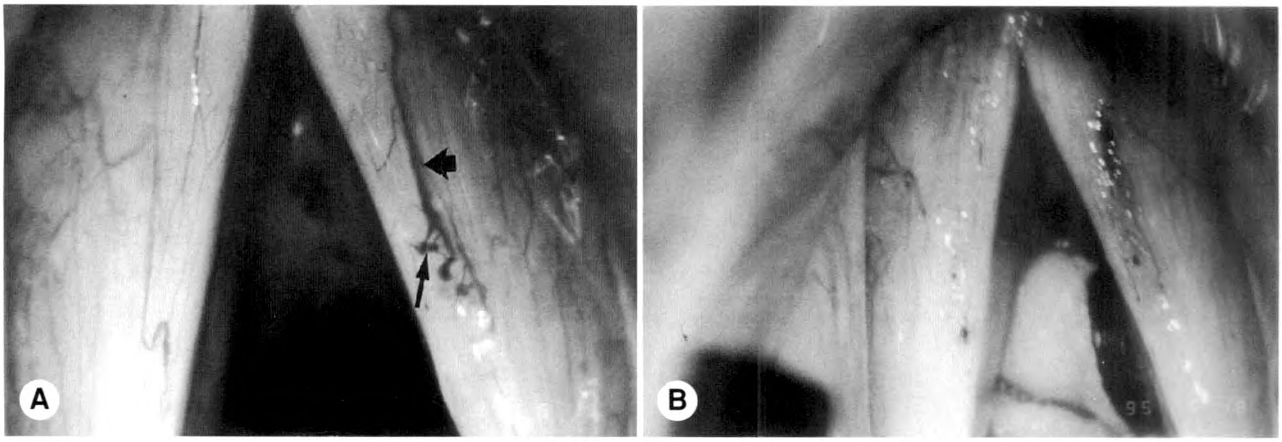


Fig 2. Another classical vocalist with history of recurrent vocal hemorrhage. A) Number of microvascular lesions are noted primarily in striking zone. Dilated varix (wide arrow) is connected to several papillary ectasias (narrow arrow) and associated spider telangiectasias. Papillary lesions were observed to show arterial pulsation. B) These microvascular lesions were ablated with carbon dioxide laser.

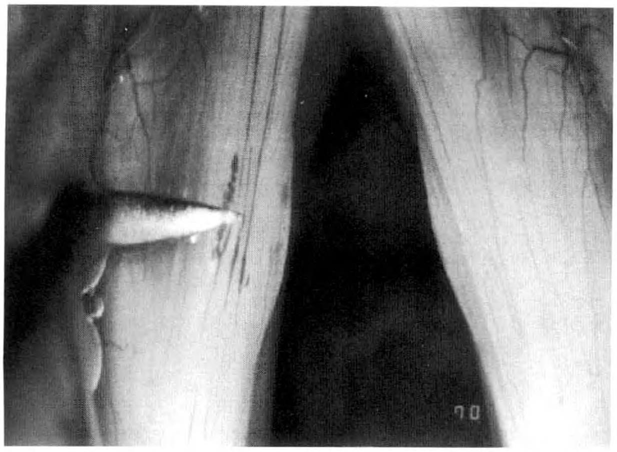


Fig 3. Tortuous varix in striking zone of third classical vocalist with history of recurrent vocal hemorrhage. Sharp angled pick is placed through epithelial cordotomy just under varix. Blood flow through varix is well seen, and tip of pick is seen through translucent membrane.

les of thin filaments that are adjacent to the luminal cell membrane. Further, the basement membrane of the microvasculature has a lamellate structure with interspersed myocytes and pericytes. These cellular filaments and buttressed basement membranes serve as a structural lattice that stabilizes the vessel wall amid the extreme shearing forces generated by high-pressure phonation.[15]

Despite the structurally stabilizing characteristics of the walls of the microvasculature of the SLP, these vessels still develop altered conformations that result in Es and Vs. These Es and Vs have long been observed to rupture more easily than normal-appearing vessels.[5] The exact interrelationship between Es and Vs and other benign masses such as nodules and polyps is unknown.

The initial surgical treatment for laryngeal hemorrhage was cautery.[1-3] Baker[5] did describe cold instrument removal without the surgical microscope. Kleinsasser[16] has long since managed these lesions by means of cold instrument dissection. Over time, the carbon dioxide (CO_2) laser became the primary modality for microvascular ablation subsequent to its introduction by Jako,[17] Strong and Jako,[18] and Vaughan.[19] However, in recent years, cold instrument phonomicrosurgical techniques have enjoyed expanded application in the management of a variety of benign vocal fold disorders.[20] With improved microinstrumentation, during the last 3 years, the authors (S.M.Z., R.T.S.) mostly abandoned the CO_2 laser for the management of Es and Vs and resumed cold instrument dissection for these lesions with the hope that this approach would provide improved precision. This collaborative study from 2 centers analyzed 1 of the largest series of vocal fold Es and Vs presented to date, and includes the assessment of surgical treatment using the CO_2 laser and/or cold instruments.

MATERIALS AND METHODS

A retrospective review was performed of all microlaryngeal procedures done by the authors in which Es and Vs were either ablated by the CO_2 laser or excised by cold instruments. The laryngoscopic exposure technique has been described previously.[21] When the CO_2 laser was used, the power was set to 1.0 to 2.0 W with a defocused spot in a single pulse mode and a pulse duration of 0.05 to 0.1 second (Fig 2). Since 1995, a cold instrument technique was applied in many cases in order to allow greater precision and less thermal injury to surrounding healthy tissue.[20] In this technique, an epithelial cordotomy is performed directly over the site of the vascular lesion regardless of its location. A sharp angled pick or needle is then used to dissect the lesion from the SLP (Fig 3) and microforceps and/or microscissors are used to excise it (Fig 1B). Bleeding is typically controlled with a topical solution of saline with 1:1,000 to 1:10,000 epinephrine. It is not uncommon for patients to have 2 to 4 separate incisions in 1 vocal fold involving both the medial and superior surfaces. The epithelial cordotomy is then allowed to heal primarily. Patients are placed on complete voice rest subsequent to the procedure for 7 to 14 days and limited voice use for the next 10 to 14 days, depending on the rate of the patient's healing. Most patients were treated for pharyngolaryngeal reflux with proton pump inhibitors, as well as with diet and behavioral management. All performers received vocal rehabilitation with a speech-language pathologist who has formal singing training, or a team including a speech-language pathologist and a singing voice specialist.

The medical records and the preoperative and postoperative strobovideolaryngoscopy (SVL) findings of these patients were reviewed. Demographic and occupational information was compiled, while intraoperative findings were correlated with preoperative and postoperative SVL findings. The SVL findings were reviewed and graded according to a standard scoring sheet, and the postoperative score was compared to the preoperative one. Parameters for analysis included location of lesion(s), glottal closure, and phase symmetry, as well as mucosal wave amplitude and magnitude.

RESULTS

Fifty patients underwent surgical management of vocal fold Es and Vs by the authors during the last 5 years. In 42 patients, preoperative and postoperative clinical and SVL records were available for review.

There were 34 women and 8 men ranging in age from 9 to 51 who presented with vocal symptoms for an average of 7 months. Thirty-nine of the 42 patients were professional or semiprofessional singers or student singers, and the other 3 were garrulous vocal abusers. The singers were classified as follows: 17 classical, 16 pop or rock, and 6 musical theater.

Recurrent vocal hemorrhage was the main indication for surgery (group 1) in 10 of 42 patients (all singers). Seven of these 10 had other concomitant benign vocal fold disorders. In 32 of 42 (group 2) patients, the primary indication for phonomicrosurgical intervention was to resect a benign lesion(s) separate from the observed Es and Vs. Twenty-nine of these 32 were singers. Despite the fact that a lesion was the indication for surgery in this group, 10 of the 32 also had a history of vocal fold hemorrhage. The concomitant lesions in the 42 patients included 36 nodules or masses, 11 polyps, 15 cysts, and 3 scars.

In the 42 patients, a total of 87 Es and Vs were treated, and 67 (77%) of these occurred on the superior surface of the vocal fold. Fifty-six (64%) of these were located at the lateral extent of the mucosal wave, as demonstrated during SVL. Only 20 (23%) of the Es and Vs occurred on the medial surface of the vocal folds. Seventy-two of the 87 (83%) Es and Vs were located in the middle third of the musculomembranous vocal fold (the striking zone).

The Es and Vs were ablated exclusively with the CO_2 laser in 13 of the 42 patients, while cold instruments were used exclusively in 23 of the 42 patients. A combined approach was employed in 6 of the 42, whereby the CO_2 laser was used to vaporize superolateral lesions and cold instrument dissection was done for lesions near or on the vibratory margin.

A new diagnostic finding in the form of observable pathologic changes was made during the microlaryngoscopy, which was not evident on preoperative flexible or rigid SVL, in 27 of the 42 (64%) patients. The surgical procedure was modified accordingly in all of these cases. Early postoperative laryngoscopic examinations were available in 21 of the 42 patients. This revealed that healing of the cold instrument epithelial cordotomy appeared complete between 4 and 10 days, whereas the healing time of the laser-treated epithelium ranged from 14 to 21 days.

The long-term follow-up on the entire group (42 patients) ranged from 3 to 33 months, with an average of 11 months. The average follow-up was 14 months in the 10 patients in whom the indication for surgery was recurrent hemorrhage. Postoperative hemorrhage occurred in 2 of the 42 patients. One was a pop music performer who attempted a performance (against medical advice) 72 hours after phonomicrosurgical intervention for a history of >5 previous hemorrhages. The other (a classical singer) underwent excision of vocal nodules and a varix. Her nodules recurred and a new varix formed, which bled 14 months following her initial surgery. She underwent a second, similar procedure and is now singing normally and has not sustained a new hemorrhage in 6 months. There were no problems with devitalization of the delicate SLP from the cold instrument dissection and resection of the microvasculature.

Stroboscopic Assessments. Postoperative glottal closure during modal voice phonation was better than on the preoperative SVL in 22 patients, and the same in 20 patients. Mucosal wave amplitude was improved (increased) in 20 patients, unchanged in 18, and worse in 4. Mucosal wave magnitude improved in 17 patients, remained the same in 22, and decreased in 3. Oscillatory phase symmetry improved in 13 patients, remained unchanged in 26, and worsened in 3. Wherever substantially decreased oscillatory characteristics of the epithelium were noted, an excision of a mass had been performed and a CO_2 laser had been used to treat the Es and Vs. In 1 of these cases, a hypertrophic scar formed on the superior surface in the region in which a CO_2 laser had been used to ablate a varix.

DISCUSSION

Presentation of Ectasias and Varices. Ectasias and varices of the musculomembranous vocal folds and accompanying hemorrhage presented most frequently in female singers. Thirty-four of the 42 patients with Es and Vs were women. Further, 16 of 19 (84%) patients with documented hemorrhages were female, and 18 of 19 (95%) were professional singers. These findings are similar to those in the 3 patients reported by Baker.[5] This demographic profile supports the fact that vascular malformations may be hormonally related, as previously suggested.[12,22,23] However, this hypothesis has not been tested. It is also possible that the gender difference is related to differences in vocal fold anatomy and associated mechanics of sound production.

The observation that the preponderance of Es and Vs are geographically in the middle of the musculomembranous vocal fold, and most frequently on the superior surface, has been noted by a number of authors.[5,7] We could not locate evidence to suggest a greater concentration of microvascular structures on the superior surface of the vocal fold. The SVL analysis provided further clues as to the genesis of Es and Vs of the vocal folds. In this series, 57 of the 87 (66%) Es and Vs were found in the region of the superolateral extent of the mucosal wave on SVL.

One possibility for why most Es and Vs tend to occur in this region is that this may be the point at which maximum shearing forces are generated within the SLP as the mucosal wave reaches its superolateral end point, decelerates quickly, and reverses direction to begin the closing phase of the oscillatory cycle. This whiplash-like effect and the limitation of the microvasculature by the basement membrane of the epithelium are probably responsible for the preponderance of hemorrhages and Es and Vs that are observed on the superior and lateral surfaces near the middle of the musculomembranous vocal fold.

We now refer to the middle of the musculomembranous fold as the **striking zone** because of the preponderance of phonatory-induced traumatic lesions of the vocal fold (Es and Vs, nodules, and polyps) to be found in this region. It was not uncommon to encounter Es and Vs during the phonomicrosurgical management of other lesions, for which there appeared to be a common element of traumatic phonation. The exact relationship between Es and Vs and other concomitant benign pathologic findings is unknown, but we believe that all of the pathologic tissue should be resected if it can be done safely. Further, the surgeon and the patient must be prepared to find and treat pathologic tissue that becomes evident during the microlaryngoscopy and was not clearly discernible during the preoperative evaluation.

Cause of Ectasias and Varices and Rationale for Treatment. Ectasias and varices probably result from chronic mechanical trauma to the microvasculature of the vocal folds. As already noted, the majority of Es and Vs occurred in the striking zone (mid-musculomembranous vocal fold). Collision forces probably make a major contribution to the formation of Es and Vs on the medial surface of the vocal folds. The fact that most Es and Vs are found on the superior surface of the striking zone may, at first glance, seem paradoxical. This observation is believed to reflect the occurrence of maximum shearing stresses in this region of the vocal folds during oscillation.

The traveling wave inertial forces on the SLP soft tissues at wave termination may be analogous to those of a whip. This relates to the soft tissue surrounding the vessel, as well as the fact that the vessel lumen contains blood, which has an independent velocity. When the vocal fold reaches its most superolateral excursion, the superficial vessels are limited by the epithelium, which results in an accumulation of force similar to the crack of a whip. Therefore, these microvascular injuries on the superior surface of the vocal fold are analogous to a whiplash injury. These vessels are less likely to sustain trauma when they are deeper within the SLP, because the substance of the SLP provides some shock absorption.

It is extremely fortunate that the majority of Es and Vs are geographically positioned just under the basement membrane of the epithelium and on the superior surface of the vocal fold. Their superficial nature facilitates easy surgical accessibility with minimal disturbance of normal SLP. This ultimately allows for rapid healing and normal vocal fold oscillation in most cases. Further, if any fibrosis does occur, it is of less significance on the superior surface of the vocal fold.

Assessment of Surgical Technique. Baker[5] introduced the concept of direct laryngoscopic excision of Es and Vs of the vocal folds in 1962. After the introduction of the CO2 laser into endoscopic laryngeal surgery in the early 1970s,[17-19] it was adopted for the treatment of Es and Vs.[7,22-24]

From general observations of high-magnification tangential dissection within the SLP, the authors developed concern that the CO2 laser was creating scarring that resulted in a stiff vocal system.[20] In addition, many Es and Vs occur on or near the valving medial edge of the vocal fold. These concerns led to the development of a cold instrument dissection technique to excise these lesions. The results of this approach demonstrate a number of advantages over the CO2 laser.

Epithelial cordotomies can be performed directly over the Es and Vs, and the aberrant vessel(s) can be dissected and excised with an angled pick, forceps, cups, or scissors. Any bleeding can be controlled easily with the application of topical epinephrine. The epithelial cordotomy, which is allowed to heal primarily, allows drainage of blood out of the vocal fold mucosa and prevents the formation of postoperative subepithelial hemorrhages. In the 23 patients in whom this technique was used, epithelial healing was complete by the 10th postoperative day without any localized stiffness as assessed by SVL. In contrast, in the 3 cases of CO2 laser ablation of Es and Vs for whom early follow-up was available, the healing time was longer, with significant local inflammation.

Further, 4 of the 19 patients treated with the CO2 laser demonstrated significant stiffness on postoperative SVL. Although all of these patients underwent concurrent phonomicrosurgical resection of associated vocal fold masses, which may have also contributed to the postoperative stiffness, significant stiffness was not encountered in the 23 patients in whom a laser was not used. This suggests that the thermal energy generated by the CO2 laser within the delicate tissues of the SLP may lead to fibrosis and attendant stiffness of the overlying epithelium.[20]

Multiple epithelial cordotomies are done with the cold instrument technique, which allows direct access to the Es and Vs and facilitates maximal preservation of normal epithelium and normal SLP. This has resulted in uneventful healing manifested by normal epithelial vibration regardless of the number or location of the incisions. The postoperative vibratory characteristics of the vocal fold epithelium, and in turn, the patient's vocal quality are dependent on minimizing trauma and disturbance of normal SLP. Up to 6 incisions were performed in a single patient without any undesirable sequelae. Similarly, 12 patients underwent excisions of Es and Vs from the medial edge of the vocal folds without untoward effect.

The excision of these delicate vessels is not detrimental to the blood supply of the vocal folds, due to the presence of a rich network of anastomosing vessels.[13,14] Excising the abnormally structured microvasculature in the striking zone may allow for a slight redistribution of the microcirculation away from this injury-susceptible region and thus decrease the risk of recurrent hemorrhage. The redistribution of the vasculature to a more favorable location is analogous to removal of varicose veins of the lower extremity. The low recurrent hemorrhage rate in group 1 (patients with a history of recurrent vocal fold hemorrhage) supports the efficacy of this method.

This review highlights the observation that Es and Vs are frequently noted in association with other traumatic vocal fold lesions. It is difficult to delineate an etiologic pathway between these disorders. The clinician is left to conjecture which occurred first. Regardless, this information does not alter the clinical microsurgical management.

CONCLUSIONS

1. Ectasias and varices are most commonly located in the middle of the musculomembranous vocal fold (striking zone) within the SLP. They occur most frequently on the superior vocal fold surface, and we believe that deceleration forces involved in vocal fold oscillation create a whiplash-type injury to the microvasculature.

2. Ectasias and varices are most commonly observed in female vocalists.

3. Mucosal wave vibration remained the same or improved in all patients who underwent cold instrument resection of Es and Vs.

4. Phonomicrosurgical removal of Es and Vs from the injury-prone striking zone appears to be effective treatment for these lesions. We believe that the success of this technique is based on redistribution of the microvasculature out of the striking zone. Longer follow-up is necessary to confirm the efficacy of this approach.

REFERENCES

1. Fraenkel B. Laryngitis Haemorrhagica. Berl Klin Wochenschr 1874;2:16-8.

2. Hartmann JH. Laryngeal hemorrhage. Trans Am Laryngol Assoc 1879;1:275-8.

3. Porter W. Hemorrhage from the larynx. NY Med J 1889; 50:315-7.

4. Lewin G. Allg Med Central Zeitung 1861;30:654.

5. Baker DC. Laryngeal problems in singers. Laryngoscope 1962;72:902-8.

6. Stedman T. Stedman's medical dictionary. Baltimore, Md: Williams & Wilkins, 1990.

7. Feder RJ. Varix of the vocal cord in a professional voice user. Otolaryngol Head Neck Surg 1983;91:435-6.

8. Sataloff RT. Post-hemorrhagic vocal fold polyps. Ear Nose Throat J 1993;73:883.

9. Remacle M, Degoid JC, Delos M. Exudative lesions of Reinke's space. Acta Otorhinolaryngol Belg 1996;50:253-64.

10. Sataloff R, Spiegel JR, Hawkshaw MJ, Caputo Rosen D. Vocal fold varicosities. Ear Nose Throat J 1993;72:194.

11. Courey M, Postma GN. Microvascular lesions of the vocal folds. Curr Opin Otolaryngol Head Neck Surg 1996;4:134-7.

12. Postma GN, Courey MS, Ossoff RH. Microvascular lesions of the true vocal fold. Ann Otol Rhinol Laryngol 1998;107: 472-6.

13. Nakai Y, Masutani H, Moriguchi M, Sugita M. Microvascular structure of the larynx. Acta Otolaryngol Suppl (Stockh) 1991(suppl 486):254-63.

14. Franz P, Aharinejad S. The microvascular of the larynx: a scanning electron microscopy study. Scanning Microsc 1994; 8:125-31.

15. Frenzel H, Kleinsasser O. Ultrastructural study on the small blood vessels of human vocal cords. Arch Otorhinolaryngol 1982;236:147-60.

16. Kleinsasser O. Restoration of the voice in benign lesions of the vocal folds by endolaryngeal microsurgery. J Voice 1991; 5:257-63.

17. Jako GJ. Laser surgery of the vocal cords. Laryngoscope 1972;82:2204-15.

18. Strong MS, Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO2 laser. Ann Otol Rhinol Laryngol 1972;81:791-8.

19. Vaughan CW. Transoral laryngeal surgery using the CO2 laser. Laboratory experiments and clinical experience. Laryngoscope 1978;88:1399-420.

20. Zeitels SM. Laser versus cold instruments for microlaryngoscopic surgery. Laryngoscope 1996;106:545-52.

21. Zeitels SM, Vaughan CW. "External counterpressure" and "internal distension" for optimal laryngoscopic exposure of the anterior glottal commissure. Ann Otol Rhinol Laryngol 1994;103:669-75.

22. Abitbol J. Vocal fold hemorrhages in voice professionals. J Voice 1988;2:261-6.

23. Lin P, Stern JC, Gould WJ. Risk factors and management of vocal fold hemorrhages. J Voice 1991;5:74-7.

24. Spiegel J, Sataloff RT, Hawkshaw MJ, Caputo Rosen D. Vocal fold hemorrhage. In: Sataloff RT, ed. Professional voice: the science and the art of clinical care. San Diego, Calif: Singular, 1997:541-54.

≈

MENIERE'S DISEASE

The Fourth International Symposium on Meniere's Disease will be held in Paris, France, April 11-14, 1999. For information, contact Administrative and Scientific Secretariat, SOCFI/MENIERE '99, 14 rue Mandar, 75002 Paris, France; telephone 33 (0) 1 44 88 25 25; fax 33 (0) 1 40 26 04 44; e-mail fournier@socfi.fr.

≈

OTOPLASTY AND RECONSTRUCTION OF AURICULAR DEFECTS

The International Course on Otoplasty and Reconstruction of Auricular Defects will be held in Lübeck, Germany, March 21-22, 1999. For information, contact PD Dr Dr R. Siegert/M. Haase, Department of Otorhinolaryngology and Head and Neck Plastic Surgery, Medical University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany; telephone +49-451-500-3189; fax +49-451-500-4192; e-mail: Sigert@medinf.mu-luebeck.de.

Ann Otol Rhinol Laryngol 108:1999

ABLATION OF TEFLON GRANULOMAS IN THE CANINE LARYNX WITH THE FREE-ELECTRON LASER

CHARLES F. LANO, JR, MD
LOU REINISCH, PHD
ROBERT H. OSSOFF, DMD, MD
C. GAELYN GARRETT, MD
TIMOTHY KUO
G. LEE BRYANT, JR, MD
JAY A. WERKHAVEN, MD
NASHVILLE, TENNESSEE

This study develops a canine model for the treatment of laryngeal Teflon granulomas and demonstrates endoscopic ablation using the free-electron laser (FEL) set at a wavelength of 8.5 μm. Laryngeal Teflon granulomas may cause dysphonia and airway obstruction, and they are difficult to remove. The infrared absorption spectrum of Teflon reveals a strong absorption peak centered at 8.5 μm. In this study, 12 dogs had the right vocal cord injected with Teflon paste. Two months later, Teflon granuloma formation was confirmed histologically. Laser incisions into the granulomas were performed at 3 different wavelengths: 7.4 μm (FEL), 8.5 μm (FEL), and 10.6 μm (carbon dioxide laser). Histopathologic analysis was performed at 1 week and 6 weeks after the laser incisions. The FEL at the 8.5-μm wavelength was found to optimally ablate the Teflon granulomas, but the granulomas persisted in the specimens treated with 7.4 μm (FEL) and 10.6 μm (carbon dioxide laser).

KEY WORDS — canine larynx, carbon dioxide laser, free-electron laser, Teflon granuloma, vocal cord paralysis.

INTRODUCTION

Teflon (EI Du Pont de Nemours & Co, Inc, Wilmington, Del) is the trade name for polytetrafluoroethylene [$(C_2F_4)_N$]. Polytef (Mentor O & O, Inc, Santa Barbara, Calif) paste contains Teflon that has been treated and pulverized to a powder in which 85% of the particles are between 5 and 95 μm in diameter. Polytef paste is 50% Teflon suspended in 50% glycerin by weight.

In 1962, Arnold[1] first described the injection of Polytef paste for the treatment of paralytic dysphonia. A unilateral paralyzed vocal fold frequently lies in the paramedian position, creating a gap between the two vocal folds during adduction. This gap may result in a weak, breathy voice and aspiration. Arnold described the injection of Teflon lateral to the vocal process, between the inner perichondrium of the thyroid cartilage and the thyroarytenoid muscle, to move the paralyzed vocal fold toward the midline. This medialization provides the mobile vocal fold an opposing surface to contact, thereby restoring the voice and eliminating aspiration. Arnold originally noted that tissue tolerance to Teflon was good, that postoperative reactions were minimal, and that there was lasting vocal improvement. He concluded that Polytef paste was the most suitable substance at that time for augmenting a paralyzed vocal fold. Several other early studies endorsed Polytef paste as a relatively safe, nonreactive substance.[2-7]

More recently, however, there have been many problems reported with the use of Teflon in the larynx.[8-10] One of the most significant problems is the formation of a Teflon granuloma.[11-14] Teflon granulomas are classically described as islands of Teflon particles dispersed among strands of fibrous tissue, infiltrated with inflammatory cells and containing numerous multinucleated giant cells.[11] Teflon granulomas may cause many undesirable symptoms such as dysphonia, airway obstruction, chronic cough, dysphagia, odynophagia, and a globus sensation.[12,13] Other problems associated with laryngeal Teflon injections include the local spread of Teflon,[15,16] migration to regional lymphatics,[17] vocal fold stiffening,[10] and technical problems (ie, excess injection or misplaced injection).[8,13] These undesirable qualities led Flint et al[16] to conclude that of the materials available today for vocal fold augmentation, Teflon is the least desirable. Currently, numerous other injectable substances are available for vocal fold augmentation, including autogenous fat, Gelfoam paste, and colla-

---

From the Department of Otolaryngology, Vanderbilt Bill Wilkerson Center for Otolaryngology and Communication Sciences, Vanderbilt University Medical Center, Nashville, Tennessee. This work was supported, in part, by a grant from the Department of Defense for the Medical Free-electron Laser Program, administered by the Office of Naval Research under grant number N0001-494-11023. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Vanderbilt University.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, May 9-10, 1998.

CORRESPONDENCE — Lou Reinisch, PhD, Dept of Otolaryngology, S-2100 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232-2559.

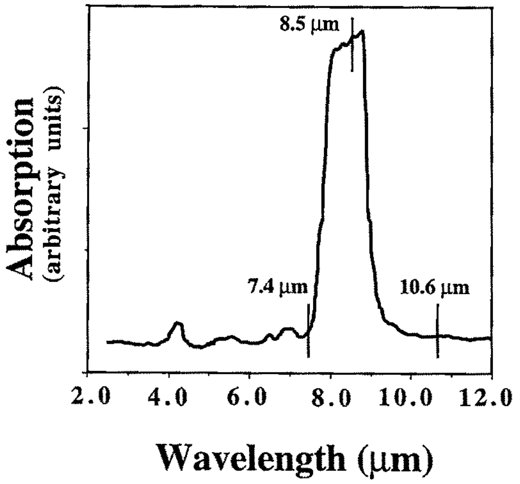


Fig 1. Absorption spectrum for polytetrafluoroethylene shown in mid-infrared region.

gen.[18,19] Medialization laryngoplasty with or without arytenoid adduction is now widely considered to be the procedure of choice for managing permanent vocal fold paralysis.[20-23]

There are many endoscopic techniques described for the removal of Teflon granulomas.[12,24-27] Despite the variety of techniques, none is universally successful. Many authors agree that removing Teflon is a tedious, challenging problem that can be an unsatisfying experience for the patient and the surgeon.[12,13]

The carbon dioxide (CO2) laser is widely used for numerous applications in otolaryngology, but has had limited success for the endoscopic removal of Teflon granulomas.[12,14,25] The CO2 laser causes a bright "welder's flash" when it impacts Teflon particles, and it inefficiently and imprecisely melts Teflon. This inefficiency can be readily explained by examining the infrared absorption spectrum for polytetrafluoroethylene (Fig 1).[28] The peak absorption for Teflon is centered around 8.5 µm, but absorption falls off to a minimal level at wavelengths shorter than 7.6 µm or longer than 9 µm. The wavelength emitted by the CO2 laser, 10.6 µm, is much longer than the absorption peak for Teflon.

The free-electron laser (FEL) is a physically large experimental laser that can generate any wavelength from 2 to 9.5 µm, allowing investigators to study the effects of a specific wavelength. The light beam emitted from the FEL is a collimated, coherent beam of monochromatic light. The lasing medium is an electron beam accelerated to 35 to 42 MeV. The electron beam is a 5-microsecond pulse of electrons traveling near the speed of light. This beam of electrons is directed through an array of magnets with alternating magnetic fields. As the beam passes through the alternating magnetic fields, it wiggles or undulates, thus producing the light. The wavelength of the laser light is selected by adjusting the distance between the permanent magnets.

With the FEL tuned to a wavelength of 8.5 µm, Teflon granulomas can be selectively and easily ablated from the hind-limb musculature of rats.[29] In this study we developed an animal model for the treatment of canine laryngeal Teflon granulomas. The purpose of this study is to evaluate the use of the FEL, tuned to wavelengths of 7.4 and 8.5 µm, and to evaluate the use of the CO2 laser at 10.6 µm, for ablating canine laryngeal Teflon granulomas.

In our earlier work, we showed that Teflon granuloma was acutely left with a 5- to 40-µm zone of thermal damage lateral to the laser incision when 8.5-µm light was used. This was in strong contrast to the 20 µm of char, 400 µm of thermal damage, and 1,000 µm of vacuolization lateral to the laser incision left when 10.6-µm light was used.[29] In this study we are interested in the healing in the vocal fold after these incisions are endoscopically made. We designed the study to create incisions in the Teflon granuloma instead of attempting to remove the granuloma. In this way, we could assess the healing when some Teflon remained in the vocal fold.

MATERIALS AND METHODS

Twelve mongrel dogs weighing between 19 and 26 kg were used for this project. Prior to each operation, each animal was premedicated with butorphanol tartrate 0.05 mg/kg and atropine sulfate 0.05 mg/kg intramuscularly. Telazol (tiletamine hydrochloride and zolazepam hydrochloride) 2 to 4 mg/kg and xylazine hydrochloride 0.275 mg/kg were used intravenously to maintain anesthesia during the operations.

Initially, all 12 dogs underwent suspension direct microlaryngoscopy with an Ossoff-Karlan modified Dedo microlaryngoscope. A 19-gauge straight Arnold injection needle was attached to a Brünings syringe for the injection procedure. A total of 0.6 mL Polytef paste, in 3 "clicks" from the Brünings syringe, was injected lateral to the right thyroarytenoid muscle of each animal.[8]

PILOT DOG

One pilot animal was painlessly sacrificed 2 months after the injection to establish the development of Teflon granulomas in the canine larynx at this time interval. As in each nonsurvival operation, this animal was premedicated and then euthanized with thiopental sodium 300 mg/kg intravenously. We harvested the larynx of this pilot animal and removed the right vocal fold. Two-millimeter-thick serial sec-

TABLE 1. SCHEDULE OF DOGS HARVESTED AFTER LASER INCISION IN TEFLON GRANULOMA FOR THREE DIFFERENT WAVELENGTHS STUDIED

	Wavelength and Laser		
	7.4-μm FEL	*8.5-μm FEL*	*10.6-μm CO_2*
1 week	2	2	2
6 weeks	2	2	1

Data are number of dogs.

FEL — free-electron laser, CO_2 — carbon dioxide laser.

tions of the right vocal fold were preserved in 10% formalin and prepared for histologic examination with hematoxylin and eosin (H & E) and Masson's trichrome stains. Histopathologic confirmation of the development of a Teflon granuloma was documented by comparing the experimental slides with slides from human vocal fold Teflon granulomas.

STUDY DOGS

Laser Incisions. The remaining 11 dogs underwent suspension direct microlaryngoscopy 2 months after the Teflon injection. Three different laser wavelengths were studied (Fig 1). We used 7.4 μm (shorter than the absorption peak), 8.5 μm (centered at the absorption peak), and 10.6 μm (longer than the absorption peak). The appropriate laser — the FEL for 7.4 μm and 8.5 μm and the CO_2 laser for 10.6 μm — was used to make an incision into the previously injected right vocal fold. The Unimax model 2000 micromanipulator (250-μm spot size), manufactured by Reliant Technologies Inc (Foster City, Calif), was used with each laser.

The FEL was used at 20 Hz (20 macropulses/s) and at its maximum power output, which was 8 to 11 mJ/macropulse. The FEL pulse structure is composed of 5-microsecond macropulses with approximately 14,000 micropulses, lasting 1 picosecond, in each macropulse. Each macropulse is separated from the next macropulse by a relatively long time interval (50,000 microseconds). Similarly, within each macropulse the micropulses are separated from the next micropulse by a relatively long time interval (350 picoseconds). Power surges during each micropulse to 750,000 W. The average intensity for the FEL was 0.2 W. The average power density was 400 W/cm^2.

The CO_2 laser (Sharplan 1060; Laser Industries, Ltd, Tel-Aviv, Israel) was set in repeat pulse mode, with pulse duration of 0.2 seconds on and 0.5 seconds off. The power was set at 5 W. The average intensity was 1.4 W. The average power density was 2,800 W/cm^2.

Each laser incision was made on the superior surface of the vocal fold overlying the granuloma. The laser was then used to divide the submucosal tissue and expose the granuloma. Next, the laser was used to ablate the substance of the Teflon granuloma. Neurosurgical pledgets moistened with 1:10,000 epinephrine hydrochloride were used to control bleeding. For each different wavelength, we closely observed and recorded the ability to cut through soft tissues of the larynx, the ability to ablate the Teflon granuloma, and the ability to provide hemostasis. Endoscopic photodocumentation was obtained with a 0° Hopkins rod telescope coupled to a 35-mm camera.

Laryngeal Harvest. There were 2 groups of dogs. One group was harvested at 1 week after the laser incisions; the other group was harvested at 6 weeks after the laser incisions. The 11 study animals were harvested according the schedule presented in Table 1. The larynges were split posteriorly, and endolaryngeal photographs were taken with a 35-mm camera at each harvest. The right vocal fold was removed, sectioned, preserved, and evaluated histologically as described above for the pilot animal.

RESULTS

PILOT DOG

Gross Appearance. The pilot dog was sacrificed 2 months after the Teflon injection to document the formation of a Teflon granuloma at this specific time interval. A granuloma was noted in the gross specimen. It was a large, red, ovoid mass involving the vocal fold and partially filling the ventricle. The mucosa overlying the mass was friable with a coarse, grainy texture. Figure 2A demonstrates an endoscopic photograph of the pilot dog's larynx.

Histopathology. The Teflon granuloma of the right vocal fold of the pilot dog was similar to a classic human Teflon granuloma. There was a large circular mass surrounded by a thin fibrous capsule. Within the mass, Teflon particles were interspersed among strands of fibrous tissue and abundant multinucleated giant cells (Fig 2B). The multinucleated giant cells contained phagocytosed Teflon particles that appeared birefringent with light microscopy (Fig 2C).

STUDY DOGS

Endoscopic Evaluation. A summary of the endoscopic observations made during the laser incisions is displayed in Table 2. In each animal, the Teflon granuloma was easily identified during endoscopy. Its appearance was similar to that in the pilot animal shown in Fig 2A. A blunt probe was used to palpate the Teflon granulomas, which were firm and rubbery.

With the 7.4-μm wavelength, the FEL was not effective for incising soft tissues, and hemostasis was

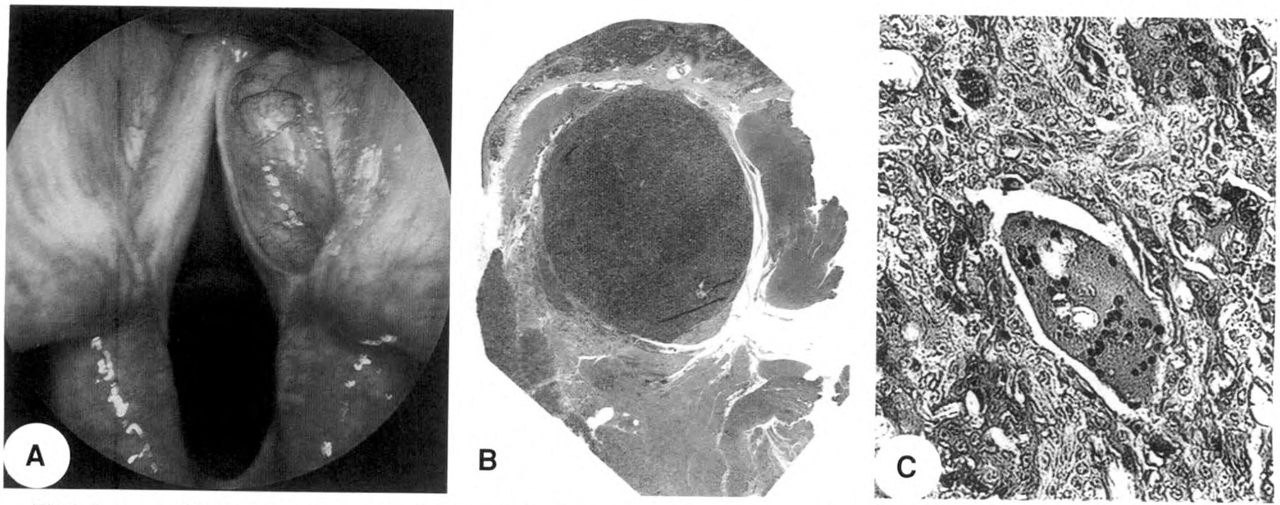


Fig 2. Laryngeal Teflon granulomas in pilot dog. A) Endoscopic photograph, 2 months after injection of Teflon. B) Histopathology, 2 months after injection of Polytef paste (H & E, original ×25). C) Multinucleated giant cell within granuloma, demonstrating phagocytosed Teflon particles (H & E, original ×100).

poor. At this wavelength, it was difficult to ablate through the mucosa and submucosa overlying the granuloma. The pale, rubbery substance of the Teflon granuloma was eventually exposed with the assistance of some microsurgical dissection. Once exposed, the Teflon granuloma was not effectively ablated by the 7.4-µm wavelength. The laser was used for approximately 15 to 20 minutes to make the incision at this wavelength. About half of the time was used in making the incision through the mucosal covering of the Teflon granuloma. The other half of the time was used in making the incision into the granuloma.

With the 8.5-µm wavelength, the FEL was not effective for incising soft tissues, and hemostasis was poor. However, once exposed, the Teflon granuloma was easily ablated. Each successive laser blast was able to penetrate deeper, removing the majority of the Teflon granuloma. The laser was used for approximately 12 to 18 minutes to make the incision at this wavelength. Nearly all the time was used in making the incision through the mucosal covering of the granuloma. Once the Teflon was reached, the incision proceeded quickly. Less than 10% of the laser time was used in making the incision in the granuloma.

The CO_2 laser (wavelength 10.6 µm) quickly made a mucosal incision and readily divided the submucosa, exposing the Teflon granuloma. The CO_2 laser easily coagulated small, bleeding vessels. Firing the CO_2 laser at the Teflon granuloma resulted in a bright flash of light ("welder's flash"). Also, as the CO_2 laser was used on the Teflon granuloma, abundant char developed on the surface of the granuloma. Overall, the CO_2 laser was ineffective in ablating the Teflon granuloma. The laser was used for approximately 3 to 6 minutes to make the incision at this wavelength. The mucosal covering was quickly ablated. The majority of the time (2 to 4 minutes) was used in making the incision in the granuloma.

TABLE 2. ENDOSCOPIC OBSERVATIONS MADE DURING LASER ABLATION PROCESS

Wavelength (µm)	*Teflon Granuloma*	*Soft Tissue*	*Char*	*Hemostasis*
7.4	Ineffective	Ineffective	No	No
8.5	Effective	Ineffective	No	No
10.6	Ineffective	Effective	Yes	Yes

Gross Appearance at One Week. At 1 week after the laser incisions, the first group of dogs underwent laryngeal harvest. The larynges were split posteriorly, and the following observations were made prior to sectioning the right vocal fold. In the 2 dogs that underwent laser incision with the FEL set at 7.4 µm, the mucosa was well healed and the Teflon granuloma was evident as a rubbery mass. In the dogs that underwent incisions with the FEL set at 8.5 µm, the mucosa was well healed, but no granuloma was evident. The 2 dogs incised with the CO_2 laser had edema and inflammation around the incision, with small areas of ulceration where the Teflon granuloma had been incised. Visible char was noted around the incision. The majority of the Teflon granuloma persisted as a firm, rubbery mass.

Histopathology at One Week. In the animals sacrificed at 1 week after the laser incision with the FEL set at 7.4 µm, there was little evidence of penetration into the Teflon granuloma. As shown in Fig 3A, the incision was well healed and the laser had penetrated just to the surface of the Teflon granuloma. With the FEL set at 8.5 µm, the vast majority of the Teflon granuloma had been ablated (Fig 3B). The

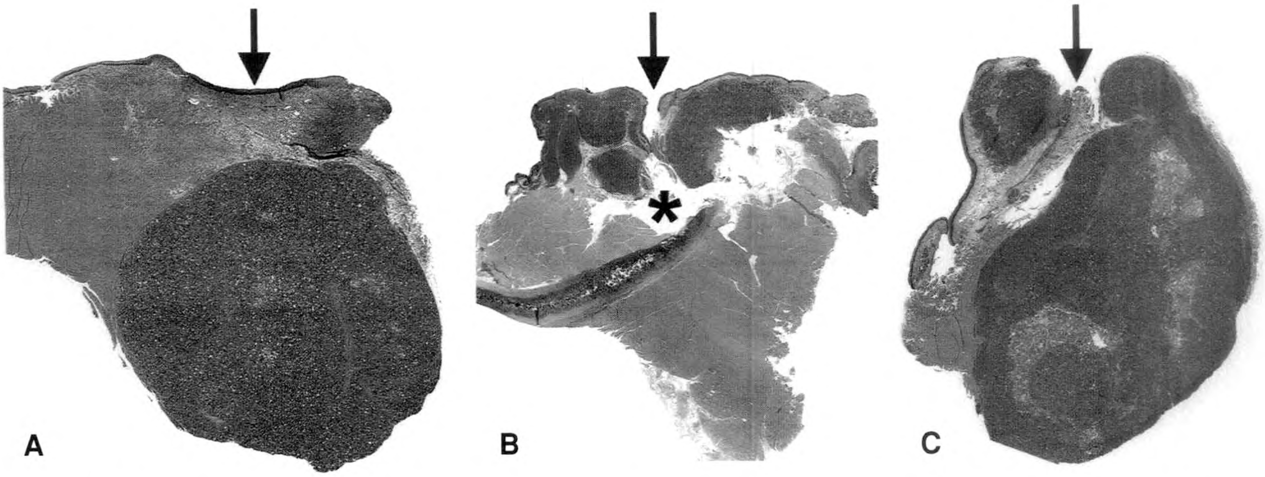


Fig 3. Teflon granulomas 1 week after laser incision (H & E, original ×40). Arrows — area of laser impact. A) With free-electron laser set at 7.4 µm. B) With free-electron laser set at 8.5 µm. Asterisk — ablated granuloma cavity. C) With carbon dioxide laser set at 10.6 µm.

CO_2 laser incision was laden with carbonaceous debris, and the majority of the Teflon granuloma remained undisturbed (Fig 3C).

Gross Appearance at Six Weeks. At 6 weeks after the laser incision, the second group of dogs underwent laryngeal harvest. By gross observation, the incisions were well healed on all the specimens. The Teflon granulomas persisted in the vocal folds incised with the FEL set at 7.4 µm and in those incised with the CO_2 laser. These Teflon granulomas had less edema and erythema compared with those seen at 1 week. The granulomas were white vocal fold masses extending up into the ventricle with a grainy appearance. Teflon granulomas were not evident in the group treated with the FEL set at 8.5 µm.

Histopathology at Six Weeks. All specimens examined at 6 weeks showed remucosalized laser incisions. The Teflon granulomas persisted in the 2 animals that underwent incisions with the FEL set at 7.4 µm and the 1 dog incised with the CO_2 laser (10.6-µm wavelength). The Teflon granulomas treated with the FEL set at 8.5 µm were ablated; only 1 very small focus of Teflon granuloma was seen on all the sections from these 2 animals.

TABLE 3. APPROXIMATE ABLATION TIMES AND ENERGIES REQUIRED TO MAKE LASER INCISIONS

	Laser Wavelength and Average Intensity		
	7.4 µm (0.2 W)	*8.5 µm (0.2 W)*	*10.6 µm (1.4 W)*
Mucosal covering			
Ablation time (min)	7.5-10	11-16	1-2
Energy (J)	90-120	132-192	84-168
Teflon granuloma			
Ablation time (min)	7.5-10	1-2	2-4
Energy (J)	90-120	12-24	168-336

DISCUSSION

The canine larynx has been used previously as an animal model to study the formation of Teflon granulomas. Ellis et al[17] demonstrated the presence of sparse giant cells with a minimal tissue reaction at 1 month after Teflon injection in the canine larynx. Kirchner et al[30] demonstrated granulomatous inflammation with giant cells as early as 6 months after injection. Our pilot animal was sacrificed and examined histologically at 2 months after injection. The histologic examination of this pilot animal demonstrated an aggressive granulomatous reaction (Fig 2B,C). The Teflon granuloma was localized and encapsulated (Fig 2B). All 12 dogs developed grossly visible Teflon granulomas by 2 months after injection. There are no previously published studies using the canine larynx as an animal model for the treatment and removal of Teflon granulomas. With standard suspension microlaryngoscopy equipment, we were able to utilize these dogs as a model for the endoscopic laser treatment of Teflon granulomas.

We studied 3 different laser wavelengths. We selected 8.5 µm due to the preliminary success with this wavelength for removing Teflon granulomas from rat muscle.[29] It happens that 8.5 µm is centered at the peak of the absorption spectrum for Teflon (Fig 1). Although this absorption spectrum does not predict variables that may occur in vivo, we used it for the basis of selecting the wavelengths in this study. We chose to study a wavelength on either side of the absorption peak: 7.4 µm (to the left of the peak) and 10.6 µm (to the right of the peak). Since the FEL is unable to generate sufficient intensities of laser light at wavelengths longer than 8.75 µm,

P24,702

we used the CO_2 laser to obtain a wavelength longer than the absorption peak for Teflon. Unfortunately, a direct comparison between the FEL and the CO_2 laser is confounded by the fact that these lasers have different pulse structures and different intensities.

We can estimate ablation efficiencies at the different wavelengths. These are estimates, since neither laser recorded the total amount of energy delivered during the procedure. We attempted to report the amount of time the laser was used. This is complicated by having to stop to reposition the microscope or to stop the bleeding. In addition, not every Teflon granuloma was at the same depth in the vocal fold. These estimates are presented in Table 3, along with the calculated laser energy delivered in this time. With all 3 wavelengths, the energy necessary to incise through the mucosal covering was 100 to 150 J. On the other hand, the granuloma required approximately twice that much energy for ablation at 10.6 μm. The 7.4-μm light, according to the Table, was more efficient than the 10.6-μm light in ablating the granuloma. Yet, the histology indicates that our incisions into the Teflon were not as deep when the 7.4-μm light was used. At 8.5 μm, the energy required for ablation clearly drops a factor of 10 or more. The histology shows large incisions, even with the lower energy. The efficiency of the 8.5-μm light in ablating Teflon granuloma is apparent.

Comparing the ablation of Teflon granulomas with the FEL at 7.4 μm to that with the FEL at 8.5 μm emphasizes the importance of the specific wavelength. The average intensity and pulse structure were the same while we used the FEL for both of these wavelengths. However, the 8.5-μm wavelength was clearly superior for ablating Teflon granulomas. This comparison indicates that the more important factor for successful ablation of the Teflon granuloma is the specific wavelength used, and not the pulse structure of the FEL. Even though the average intensity of the FEL was a factor of 7 less than that of the CO_2 laser, the FEL at 8.5 μm was able to ablate the Teflon granulomas much more effectively than the CO_2 laser. This further suggests that the ablation of Teflon granulomas was largely dependent on the 8.5-μm wavelength.

Neither of the 2 wavelengths generated by the FEL provided good hemostasis. The lack of hemostasis is probably due to the pulse structure of the FEL. The short 5-microsecond pulses of the FEL limit the lateral thermal damage and therefore do not coagulate the nearby small blood vessels. However, the CO_2 laser, a continuous-wave laser, provides a longer laser pulse duration that coagulates surrounding small blood vessels.[31] Therefore, a continuous-wave laser with wavelengths of 7.4 μm or 8.5 μm should have hemostatic qualities similar to those of the CO_2 laser.

The lower power density used with the FEL explains the difficulty encountered when incising soft tissues. The ability of a laser to incise tissue depends upon the intensity, the spot size, and the absorption coefficient. The spot sizes were the same for all wavelengths. The absorption coefficients for water are similar for each wavelength: 555 cm^{-1} (7.4 μm), 550 cm^{-1} (8.5 μm), and 640 cm^{-1} (10.6 μm).[32] The CO_2 laser was set at a common clinical setting (see Materials and Methods). The FEL was used at the maximum power that it could deliver at the given wavelengths (see Materials and Methods). The CO_2 laser had a much higher average intensity (1.4 W) than the FEL (0.2 W). If the FEL had been able to generate average intensities as high as the CO_2 laser, it would have likely produced similar soft tissue ablation.

With several improvements, the FEL could be considered for ablating Teflon granulomas in the human larynx. First, it would be helpful to have a higher intensity at the desired wavelength prior to human use. The ability of the FEL to incise soft tissue and the hemostatic qualities of these wavelengths may be improved with a higher intensity. Second, the reliability of the FEL for delivering a specific laser wavelength consistently is not optimal. This unreliability is due to a number of technical factors that need to be resolved. The optimal laser for this application would reliably generate a wavelength of 8.5 μm at high intensities.

One of the potential drawbacks to endoscopic laser removal of Teflon granulomas is the potential for production of harmful by-products. By-products from lasing materials have been traditionally difficult to measure. Halogenated polymers like Teflon are expected to yield hydrogen fluoride.[33] There are possibly other harmful by-products produced from lasing Teflon, including perfluorinated polycyclic aromatic hydrocarbons.[33] These by-products are probably in the plume when Teflon granulomas are ablated with the CO_2 laser. However, these by-products may be even more abundant when the FEL at 8.5 μm is used, since it ablates Teflon much more efficiently. Future studies to evaluate the by-products of lasing in vivo Teflon granulomas need to be performed. As always, when using lasers, appropriate laser safety precautions must be taken, including the suction removal of laser plume.

CONCLUSIONS

The FEL set at 8.5 μm is useful for the ablation of

Teflon granulomas in the canine larynx. This was demonstrated endoscopically and histopathologically. The exceptional ability of this wavelength to ablate Teflon can be predicted by studying the absorption spectrum for Teflon. This absorption spectrum also helps explain why the CO_2 laser may not remove Teflon granulomas effectively and why shorter wavelengths may similarly fail.

ACKNOWLEDGMENTS — We thank Dr Shan Huang and Mike Slowey for their technical support.

REFERENCES

1. Arnold GE. Vocal rehabilitation of paralytic dysphonia: IX. Technique of intracordal injection. Arch Otolaryngol 1962; 76:358-68.

2. Lewy RB. Responses of laryngeal tissue to granular Teflon in situ. Arch Otolaryngol 1966;83:355-9.

3. Toomey JM, Brown BS. The histological response to intracordal injection of Teflon paste. Laryngoscope 1967;77:110-20.

4. Arnold GE. Alleviation of aphonia or dysphonia. Through intrachordal injection of Teflon paste. Ann Otol Rhinol Laryngol 1963;72:384-95.

5. Arnold GE. Further experience with intracordal Teflon injection. Laryngoscope 1964;74:802-15.

6. Stone JW, Arnold GE, Stephens CB. Intracordal Polytef (Teflon) injection: histologic study of three further cases. Arch Otolaryngol 1970;91:568-74.

7. Dedo HH, Urrea RD, Lawson L. Intracordal injection of Teflon in the treatment of 135 patients with dysphonia. Ann Otol Rhinol Laryngol 1973;82:661-7.

8. Montgomery WW. Laryngeal paralysis Teflon injection. Ann Otol Rhinol Laryngol 1979;88:647-57.

9. Lewy RB. Teflon injection of the vocal cord: complications, errors, and precautions. Ann Otol Rhinol Laryngol 1983; 92:473-4.

10. Nakayama M, Ford CN, Bless DM. Teflon vocal fold augmentation: failures and management in 28 cases. Otolaryngol Head Neck Surg 1993;109:493-8.

11. Dedo HH, Carlsöö B. Histologic evaluation of Teflon granulomas of human vocal cords. Acta Otolaryngol (Stockh) 1982;93:475-84.

12. Ossoff RH, Koriwchak MJ, Netterville JL, Duncavage JA. Difficulties in endoscopic removal of Teflon granulomas of the vocal fold. Ann Otol Rhinol Laryngol 1993;102:405-12.

13. Kasperbauer JL, Slavit DH, Maragos NE. Teflon granulomas and overinjection of Teflon: a therapeutic challenge for the otorhinolaryngologist. Ann Otol Rhinol Laryngol 1993;102: 748-51.

14. Varvares MA, Montgomery WW, Hillman RE. Teflon granuloma of the larynx: etiology, pathophysiology, and management. Ann Otol Rhinol Laryngol 1995;104:511-5.

15. Boedts D, Roels H, Kluyskens P. Laryngeal tissue responses to Teflon. Arch Otolaryngol 1967;86:562-7.

16. Flint PW, Corio RL, Cummings CW. Comparison of soft tissue response in rabbits following laryngeal implantation with hydroxylapatite, silicone rubber, and Teflon. Ann Otol Rhinol Laryngol 1997;106:399-407.

17. Ellis JC, McCaffrey TV, DeSanto LW, Reiman HV. Migration of Teflon after vocal cord injection. Otolaryngol Head Neck Surg 1987;96:63-6.

18. Bauer CA, Valentino J, Hoffman HT. Long-term result of vocal cord augmentation with autogenous fat. Ann Otol Rhinol Laryngol 1995;104:871-4.

19. Ford CN, Bless DM. Clinical experience with injectable collagen for vocal fold augmentation. Laryngoscope 1986;96: 863-9.

20. Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. Acta Otolaryngol (Stockh) 1974;78:451-7.

21. Netterville JL, Stone RE, Luken ES, Civantos FJ, Ossoff RH. Silastic medialization and arytenoid adduction: the Vanderbilt experience. A review of 116 phonosurgical procedures. Ann Otol Rhinol Laryngol 1993;102:413-24.

22. Koufman JA. Laryngoplasty for vocal fold medialization: an alternative to Teflon. Laryngoscope 1986;96:726-31.

23. Maves MD, McCabe BF, Gray S. Phonosurgery: indications and pitfalls. Ann Otol Rhinol Laryngol 1989;98:577-80.

24. Horn KL, Dedo HH. Surgical correction of the convex vocal cord after Teflon injection. Laryngoscope 1980;90:281-6.

25. Koch WM, Hybels RL, Shapshay SM. Carbon dioxide laser in removal of Polytef paste. Arch Otolaryngol Head Neck Surg 1987;113:661-4.

26. Dedo HH. Injection and removal of Teflon for unilateral vocal cord paralysis. Ann Otol Rhinol Laryngol 1992;101:81-6.

27. Russell JD, Perry A, Cheesman AD. Cordectomy: a solution to Teflon granuloma of the vocal fold. J Laryngol Otol 1995;109:53-5.

28. Pouchert CJ. The Aldrich library of infrared spectra. 3rd ed. Milwaukee, Wis: Aldrich Chemical Co, 1981:1574c.

29. Bryant GL Jr, Lano CF Jr, Ossoff RH, Reinisch L, Werkhaven JA. Ablation of Teflon granuloma with the free-electron laser emitting in the eight- to nine-micron range. Ann Otol Rhinol Laryngol 1998;107:269-74.

30. Kirchner FR, Toledo PS, Svoboda DJ. Studies of the larynx after Teflon injection. Arch Otolaryngol 1966;83:350-4.

31. Reinisch L. Laser physics and tissue interactions. Otolaryngol Clin North Am 1996;29:893-914.

32. Hale GM, Querry MR. Optical constants of water in the 200-nm to 200-μm wavelength region. Appl Opt 1973;12:555-63.

33. Kokosa JM. Hazardous chemicals produced by laser materials processing. J Laser Appl 1994;6:195-201.

Ann Otol Rhinol Laryngol 108:1999

TRANSVERSE INFRAHYOID APPROACH TO BILATERAL GLOTTIC TUMORS

ANTHONY J. REINO, MD, MSC
WILLIAM LAWSON, MD, DDS
HUGH F. BILLER, MD
NEW YORK, NEW YORK

Glottic exposure and entry for vertical partial laryngectomy procedures has traditionally been through the subglottis. Although this approach is generally satisfactory for the resection of unilateral vocal cord lesions, it may be unsafe in cases in which tumors extend across the midline and/or subglottically. In these instances, we prefer the superior transverse infrahyoid approach to the glottis, which transects the petiole of the epiglottis and reflects the contents of the preepiglottic space posterior and superior. This improved visualization of the larynx has permitted precise tumor excision without sacrifice of uninvolved segments of the vocal cords. This procedure has been performed 35 times over a 15-year period at our institution for the resection of bilateral glottic tumors, with and without subglottic extension. In none of the cases in which it has been employed was there a positive surgical margin.

KEY WORDS — bilateral hemilaryngectomy, laryngeal tumors, transverse infrahyoid approach.

INTRODUCTION

The vertical hemilaryngectomy was first performed in 1875, by Billroth (see Quinn[1]), and modified by Gluck[2] in 1912 and again in 1930 by Hautant.[3] Since that time, modifications by others have resulted in partial laryngeal surgery as a viable alternative to total laryngectomy for selected T1, T2, and T3 glottic cancers.[1,4-9] The laryngeal injection studies of Pressman et al[10] and the whole organ serial section studies of others[5,11-14] provide a histologic basis for conservation laryngeal surgery.

In the past 25 years, the hemilaryngectomy procedure has been extended, and now as many as 75% of cancerous larynges may be partially resected and reconstructed. More recent refinements in reconstruction have focused on improving voice, respiration, and deglutition.

Tumors that involve the anterior commissure and both vocal cords with normal mobility can be resected by a modification of the frontolateral approach with preservation of a significant portion of 1 thyroid ala on the side of lesser involvement. The cord adjacent to the preserved thyroid ala is resected subperichondrially to prevent laryngeal foreshortening and subsequent stenosis. This subperichondrial resection is oncologically satisfactory, provided the vocal cord does not exhibit fixation, or diminished mobility, which implies vocalis muscle invasion. However, under the latter circumstances, preservation of the thyroid ala leads to an increased incidence of local recurrence.[15,16] Therefore, in larynges in which both vocal cords are involved with tumor, and decreased mobility or fixation of a cord is present, the indicated oncologic procedure requires resection of both adjacent thyroid alae. Reconstruction following bilateral thyroid ala resection must provide maintenance of the anteroposterior diameter and internal epithelial resurfacing of the larynx to eliminate the occurrence of stenosis.

Although a number of articles present in the literature describe indications, techniques, and outcome analyses of surgery for bilateral true vocal cord carcinoma, few studies emphasize the approach for resection. The traditional approach through the cricothyroid membrane into the subglottis is generally adequate for unilateral lesions; however, for lesions that involve both vocal cords, or the vocal cords and subglottis, this mode of entry is dangerous, since it is not performed under direct vision. This requires the surgeon to estimate both the thyroid lamina and soft tissue incisions from the results of laryngoscopy. Accurate laryngeal entry is important, since in many situations the planned resection will remove all glottic-level structures except the arytenoid cartilage on the less involved side. Failure to visualize the endolarynx at entry can jeopardize arytenoid integrity, necessitating total rather than partial laryngectomy. An alternative is entry into the larynx via a midline thyrotomy so that posterior glottic margins can be visualized and the specimen removed in halves; however, entry through tumor is oncologically unacceptable.

From the Department of Otolaryngology–Head and Neck Surgery, The Mount Sinai Medical Center, New York, New York.

Presented at the meeting of the American Laryngological Association, Scottsdale, Arizona, May 10-11, 1997.

CORRESPONDENCE — Anthony J. Reino, MD, MSc, 175 Memorial Hwy, Suite 1-2, New Rochelle, NY 10801.

The purpose of this paper is to introduce a new, relatively safe and uncomplicated superior approach to the endolarynx for patients with horseshoe lesions of the true vocal cords.

MATERIALS AND METHODS

A 15-year retrospective analysis was performed at The Mount Sinai Medical Center in New York on 35 patients with bilateral glottic tumors. All patients underwent bilateral hemilaryngectomy through the transverse infrahyoid approach. The age range was from 40 to 78 years with a mean of 60.2 years, and the follow-up interval was from 2 to 15 years. Men significantly outnumbered women in this study, by a ratio of 32:3. Informed consent was obtained from all patients before surgery was performed.

Although all patients were resected through our superior approach, their method of reconstruction was dependent on the size of the tumor and the extent of thyroid cartilage resection. The reconstructive methods employed were silicone keel (12 patients); epiglottoplasty (10 patients); and thyroid cartilage transposition (13 patients). Subglottic tumor extension measuring from 3 to 16 mm anteriorly, or to 1 cm posteriorly, was present in 34.7% of patients. All patients demonstrated either diminished mobility of 1 vocal cord, or vocal cord fixation. The arytenoid cartilages were removed in conjunction with a portion of the cricoid cartilage in 4 cases and by themselves in 7 patients. The margins of resection were free of tumor in all cases.

The procedures to be discussed require accurate preoperative assessment of tumor extension and therefore are indicated in a carefully selected group of patients with bilateral glottic carcinoma. The criteria for case selection include 1) tumor involving the anterior commissure and both vocal cords; 2) mobility of the cords diminished bilaterally or 1 cord fixed and the other with diminished motion; 3) subglottic involvement of less than 1.5 cm anteriorly and laterally, with under 1 cm subglottic involvement posteriorly; 4) involvement of the arytenoid limited to the vocal process and the anterior surface of the arytenoid; and 5) 1 arytenoid including the vocal process free of tumor, with no fixation on the side of arytenoid preservation. These procedures can be performed after irradiation failure in judiciously selected cases having limited subglottic extension only anteriorly; they are contraindicated when cartilage invasion is present.

The placement of a keel is indicated 1) for anterior commissure lesions with limited bilateral true cord extension in which about 1 cm of thyroid cartilage is removed from both sides and 2) for unilateral true cord lesions that have spread across the anterior commissure to the contralateral vocal cord, requiring resection of the thyroid lamina back to the oblique line on 1 side and 1 cm of cartilage resection on the opposite side. In these circumstances, a silicone keel prevents anterior webbing and stenosis. The keel should extend posteriorly between the vocal processes, and is maintained in position by 2 heavy nylon or polypropylene sutures. The keel should not impinge upon the posterior cricoid arch, to prevent erosion and bleeding. After 4 to 6 weeks, the keel is removed through a laryngoscope and the patient can be decannulated.

For larger lesions of the anterior commissure, the resection may be extended posteriorly to both vocal processes. With these lesions, the segment of anterior thyroid cartilage removed is greater than 1 cm. Although some cases may be reconstructed with the keel technique, functional results are often better postoperatively if tissue is interposed anteriorly to prevent truncating the larynx.

The epiglottic laryngoplasty, as described by Kambic[17] and Sedlacek[18] and popularized by Tucker et al,[19] may be employed with bilateral vocal cord carcinomas that require resection of the thyroid lamina to the oblique line on 1 side and halfway on the contralateral side. The reconstruction consists of grasping the epiglottis at the petiole with a tenaculum and carefully dissecting the mucosa over its lingual aspect. This requires division of the hyoepiglottic and glossoepiglottic ligaments; however, care must be taken to preserve the superior mucosal attachments of the epiglottis, where its remaining nutrient blood supply lies. The head is partially flexed and the epiglottis is displaced inferiorly into the ablative defect. The epiglottis is then systematically sutured to the thyroid ala remnants and the cricothyroid membrane with 2-0 Vicryl sutures. The musculoperichondrial flaps are then closed in 1 or 2 layers. A ½-in Penrose drain is placed in the wound and remains for 2 to 3 days. The cuff on the tracheostomy tube is left inflated for 48 to 72 hours to prevent subcutaneous emphysema.

The staged laryngoplasty procedure is performed with bilateral glottic carcinomas requiring resection of the thyroid lamina back to both oblique lines. Here, reconstruction is initiated by suturing the petiole of the epiglottis anteriorly to the infrahyoid tissues. The posterior remnants of the thyroid cartilage are mobilized by severing the cricothyroid articulation and separating the pyriform sinus mucosa from its medial aspect. The inferior constrictor muscle is left attached to the cartilage. The posterior thyroid alae are then rotated forward 90°. In order to perform this rotation, the inferior constrictor muscle is separated from

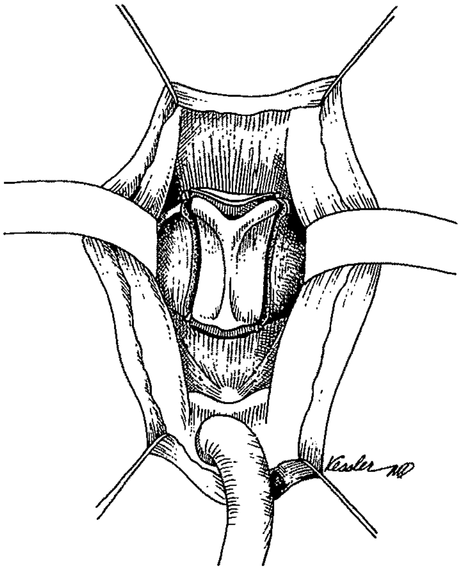


Fig 1. Preparation for superior laryngeal entry: thyroid cartilage incisions have been made through cartilage, as well as hyoepiglottic and thyroepiglottic ligaments, to release epiglottic petiole.

the superior aspect of the thyroid ala. Following rotation of the alae anteriorly, they are shortened so as to extend only slightly anterior to the cricoid arch. A 3-0 polypropylene suture passed from the cricoid to the thyroid ala stabilizes the cartilage in its new position. A small piece of cartilage is also sutured to the cricoid to replace the arytenoid if it has been resected. The skin flaps are now advanced into the operative defect and are sutured to the cut margin of the vocal process on 1 side and the mucosa over the neoarytenoid on the opposite side. The remaining skin incisions are closed in layers. A nasogastric tube is inserted and a tracheotomy tube replaces the endotracheal tube. Healing of the laryngostome is usually complete in 3 to 6 weeks. During this time, healing of the laryngeal trough is directly observed. Granulations may develop, which will require cauterization. The patient is fed on the seventh postoperative day. Aspiration into the trough is generally noted during the first few days. The time of closure of the laryngostome is determined by 1) complete healing of the suture lines; 2) absence of aspiration; and 3) adequate airway patency when the laryngostome is closed by taping. Closure of the laryngostome is performed under general anesthesia. A circumferential incision is made around the laryngostome and the skin is undermined medially and turned in, forming the first layer of the closure. The external defect is closed by rotating an adjacent cervical flap. The donor defect of this flap is either closed primarily or skin-grafted. The tracheotomy tube is removed several days later.

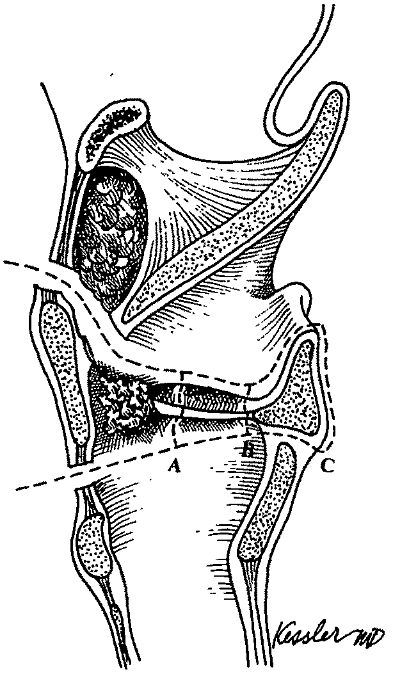


Fig 2. Release of preepiglottic space structures for posterosuperior retraction, enhanced endolaryngeal visualization, and accurate tumor resection. Letters A, B, and C demonstrate areas of possible resection based on tumor size.

Adequate exposure of the thyroid cartilage is achieved by elevation of bilateral perichondrial flaps. Parasagittal, midlamina, or oblique-line cartilage cuts are made, depending on tumor extent and vocal cord mobility as determined by direct laryngoscopy. A single hook is placed at the thyroid notch, retracting the larynx downward, and an incision is made with a No. 15 blade between the epiglottis and the upper border of the thyroid cartilage (Fig 1). The dissection is carried through the hyoepiglottic and thyroepiglottic ligaments to release the epiglottic petiole. Once the petiole is divided, the dissection is continued at the same level laterally to free the preepiglottic space structures so they may be retracted posteriorly and superiorly (Fig 2). With retraction of the contents of the preepiglottic space, the entire endolarynx is visualized, permitting accurate incision of the glottic soft tissues (Fig 3). Tumor resection begins on the side of lesser involvement, with the mucosal incision made posterior to the lesion and extended into the thyroid cartilage incision. The larynx is then rotated outward with a single hook and the cricothyroid membrane is divided at a level beneath the inferior extent of the tumor. It may even be necessary to resect a portion of the anterior cricoid arch to achieve a tumor-free margin inferiorly. The contralateral true vocal cord is similarly incised posterior to the lesion, through the thyroid cartilage incision, with Metzenbaum and right-angle scissors.

RESULTS

There were no complications associated with this

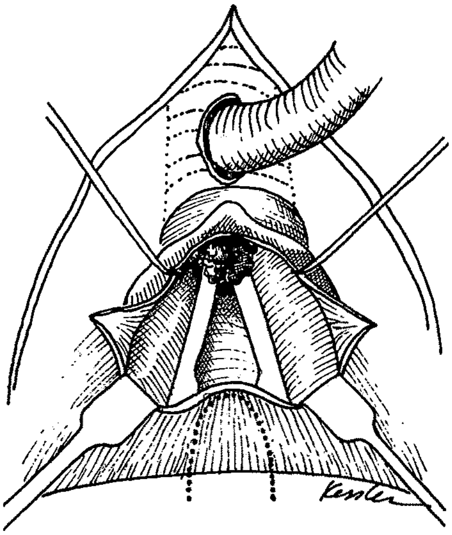


Fig 3. View from above with retraction of preepiglottic space contents.

approach. All tumors had adequate visualization, which allowed for judicious tumor resection and salvage of normal soft tissue and cartilage, and tumor-free surgical margins were achieved.

DISCUSSION

The term hemilaryngectomy encompasses many procedures and therefore is an ambiguous and inaccurate description of a technique for the total or partial removal of 1 or both vocal cords.

The anterior commissure technique of partial laryngectomy with keel reconstruction was pioneered by Kirchner and Som[20] in 1975. In their study, 58 T2 lesions of the larynx were treated by this technique and followed from 4 to 19 years. Eleven of these patients were radiotherapy failures. These authors reported a 69% long-term success rate; however, total laryngectomy was necessary for salvage in 2 patients.

In a recent study by the present authors that compared reconstructive techniques used after bilateral hemilaryngectomy (keel, epiglottoplasty, laryngoplasty), 34 patients underwent keel placement.[21] Fifty percent of the cases were staged as either T2 or T3, and there were 2 preoperative radiotherapy failures. All patients were decannulated after an average of 3 days, were swallowing within 10 days, and had an adequate voice. There were 4 local recurrences (11.7%), which developed in the following areas: postcricoid space; right pyriform sinus; anterior glottis and preepiglottic space; and subglottis. The mean time to recurrence was 23 months. All patients were treated by total laryngectomy or total laryngectomy and radical neck dissection, with a control rate of 100%.

Epiglottic reconstruction of the glottis was first described in the European literature in 1965.[17,18] In this country, Tucker et al[19] reported their experience with epiglottic laryngoplasty in 10 patients. In this series, there were no deaths and all patients were decannulated and tolerated oral feedings within 18 postoperative days. No recurrences (after a short follow-up interval) were noted, and the procedure was safely performed following irradiation failure.

In 1981, Biller and Lawson[16] reported their results with this reconstructive technique in 6 patients. They noted that with bilateral resection of the thyroid lamina to the vocal processes, a foreshortened larynx resulted. Although the patients could be decannulated, they had a marginal airway that became compromised with upper respiratory tract infections.

In the study by Reino et al,[21] 15 patients underwent epiglottic reconstruction of the larynx. Eighty-seven percent of cases were staged as T2 or T3. Although all patients were successfully decannulated and swallowing within 2 weeks, a marginal airway resulted when the thyroid cartilage resection was carried to both oblique lines. There was 1 recurrence in this group, which occurred on the remaining true vocal cord and arytenoid 18 months after the primary procedure. The patient was salvaged with a total laryngectomy.

Conley[22-25] reported the use of cervical skin flaps for laryngeal reconstruction in several publications. In 1975, he reported his results using bilateral advancement flaps from the neck in 60 patients.[22] In this study, 42 patients were reconstructed in a single stage, and 18 in 2 stages. Eight patients were radiotherapy failures, 6 had subglottic extension, 2 had posterior commissure encroachment, and 8 had greater than 90% of the glottis resected. The author reported a cure rate of 85%. The most serious complication was recurrent tumor underneath the flap with airway obstruction. This occurred in 4 patients (6.6%), with 2 salvaged by total laryngectomy and radical neck dissection. The voices of these patients were subjectively described as low-pitched and soft, with limited range.

Biller and Lawson[16] reported their initial experience in 5 patients with thyroid cartilage transposition laryngoplasty in 1981. All patients had bilateral vocal cord involvement with vocalis muscle invasion, and 4 patients had 1 arytenoid resected. With the exception of 1 death due to pulmonary embolism prior to reconstruction, all patients were free of disease and developed good airways with adequate glottic closure and satisfactory voice, with a minimum of 3 years' follow-up.

In 1997, Reino et al[21] published their results in 23 patients using the laryngoplasty technique for glottic reconstruction. Eighty-seven percent of patients were decannulated successfully within 3 weeks, and all were swallowing by 2 weeks. All patients had an adequate voice. Three patients failed decannulation. This was thought to be related to the extent of the tumor resections, all of which included a portion of the cricoid cartilage along with 1 arytenoid. The recurrence rate was 13%, with tumor appearing in the pyriform sinus, laryngostome, and supraglottis within 1 year. Two of these patients were preoperative radiotherapy failures and were salvaged with total laryngectomy and total laryngectomy with radical neck dissection. The third patient had a recurrent spindle cell chondrosarcoma that was refractory to postoperative irradiation and chemotherapy.

The approaches to the glottis may be classified into 5 categories: midline (laryngofissure); inferior (through the cricothyroid membrane); anterolateral (via pharyngotomy); combined (superior and inferior); and superior.

Buck performed the first laryngofissure and cordectomy for cancer of the larynx, in 1851.[26] Gluck,[2] in 1903, used this midline approach to develop the true vertical hemilaryngectomy; however, this operation produced profound disturbance in the protective function of the larynx.

Although midline thyrotomy allows adequate visualization of the larynx, it may only be used with small lesions of the free edge of the vocal cord that are amenable to cordectomy. It may not be used when the lesion approaches the anterior commissure.

As techniques for partial laryngeal surgery evolved, so did the approaches. Ogura and Biller[27] developed the inferior approach to the larynx, which consists of entry through the cricothyroid membrane into the subglottis. Unilateral true vocal cord lesions are easily extirpated in this manner by connecting the cricothyroid membrane incision to the anterior and posterior lamina incisions. The larynx is opened like a book by cutting the anterior soft tissue; and at the same time, the tumor is visualized and removed. For bilateral glottic lesions, the subglottis must first be examined for tumor extension. In order to avoid tumor violation, the remaining incisions are based on a previous direct laryngoscopy. The posterior cartilage incision on the less-involved side is joined with the cricothyroid membrane incision. The larynx is opened from below upward without the benefit of intraluminal visualization.

Mohr et al[28] used an anterolateral pharyngotomy to access bilateral glottic malignancies. Here, the perichondrium is reflected downward attached to the strap muscles, and a predetermined saw cut is made. The larynx is skeletonized as with a total laryngectomy, and the pyriform sinus mucosa is reflected medially. The cricothyroid joint is transected, and the anterolateral pharyngotomy is performed on the side of the lesion and extended medially. The laryngopharyngotomy is continued through the thyroid cartilage to the level of the vocal cords. This provides a good view of the glottis before the removal of tumor. We have effectively used a variation of this approach for supraglottic lesions that involve the lingual surface of the epiglottis.

In 1990, Laccourreye et al[29] reported in the American literature their results on 36 patients with the supracricoid laryngectomy and cricohyoid epiglottopexy. Stated indications for this procedure include 1) unilateral T1 glottic carcinoma with anterior commissure involvement; 2) bilateral T1 glottic carcinoma with or without anterior commissure extension; 3) T1 glottic carcinoma with multiple areas of dysplasia or hyperplasia; and 4) unilateral or bilateral T2 glottic carcinoma with or without impaired vocal cord mobility. Contraindications cited include 1) lesions originating in the ventricle or anterior commissure; 2) ipsilateral arytenoid cartilage fixation; 3) anterior or posterior subglottic extension that is more than 10 mm or 5 mm, respectively; and 4) preoperative respiratory impairment.

In the cases of Laccourreye et al,[29] the larynx is entered through a combined approach, which includes a superior transverse transepiglottic laryngotomy that transects the suprathyroid portion of the epiglottis and an inferior cricothyroidotomy. The airway is maintained through the opening in the cricothyroid membrane, and the tumor is visualized by grasping the larynx with an Allis clamp and pulling it anteriorly and inferiorly. Although the proposed advantage of this approach over the standard inferior approach is wide field exposure for tumor resection, there is little attempt to save the thyroid cartilage, which is completely removed along with the paraglottic space structures and specimen. The procedure spares the entire cricoid cartilage, most of the epiglottis, and at least 1 arytenoid.

The use of the transverse infrahyoid approach to bilateral glottic tumors was introduced by H. F. Biller at The Mount Sinai Medical Center, New York, in 1982. Quinn[30] was the first to describe superior entry into the larynx in 1969. In this approach, bilateral thyrotomies are performed before direct tumor identification. An incision is made in the thyrohyoid membrane at the thyroid notch and extended laterally along the superior border of the affected thyroid lamina to a lateral thyrotomy site. The lesion is inspected from above and the area of resection is determined. Next, the cricothyroid membrane is incised along the inferior border of the thyroid cartilage, between the inferior extents of both thyrotomy incisions. The soft tissue on the less-involved side is opened from above downward through the thyrotomy site while the tumor is viewed from above. This procedure allows for better tumor visualization before resection; however, it requires blind thyrotomy incisions before intraluminal access can be attained, and transects the suprathyroid portion of the epiglottis, which could have been used in reconstruction.

In 1995, Collins[31] reported her experience using a modification of this procedure. In this variation, a 19-gauge needle is inserted at the bottom of the thyroid notch and is angled caudad and posteriorly to emerge intraluminally between the epiglottic petiole and the anterior commissure, as confirmed by concomitant observation through a laryngoscope. The angle of the needle guides an incision that follows the superior border of the thyroid alae and internally detaches the inferolateral aspect of the epiglottis from the false vocal cords. This maneuver is likewise monitored through the laryngoscope by an observer. Internally, the knife emerges at the aryepiglottic fold level, and a full-thickness cut is made in 1 move. The aryepiglottic folds are not transected posterolaterally. The thyrohyoid membrane, preepiglottic space contents, and epiglottis may be pushed posteriorly to allow direct visualization of the glottic opening from above. With the glottic structures in view, soft tissue and cartilage cuts are made in a manner that facilitates maximum preservation of normal tissues while obtaining negative cancer margins. In the case of a scaphoid thyroid cartilage with a particularly acute alar angle, the anterosuperior thyroid cartilage may be lowered with a rongeur to provide better visualization of the true vocal cords.

Although this approach provides improved visualization of the larynx from above, it requires concomitant laryngoscopy by another individual to guide the placement of the localizing needle and the initial intraluminal incisions. This presents several problems: the surgeon is dependent on the observer's experience for guidance with needle placement and incisions; simultaneous direct laryngoscopy disrupts the surgery; and although minimal, there is increased operating time.

The transverse infrahyoid approach is easily incorporated into the surgical procedure, does not require another surgeon for guidance, and does not increase the length of the operation. It allows posterosuperior displacement of the preepiglottic space structures by transecting the petiole at its anatomic insertion and extending this incision laterally. Once these structures are detached, the entire contents of the preepiglottic space may be retracted, giving an unparalleled view of the glottis and tumor.

CONCLUSION

The ability to successfully extirpate and reconstruct large laryngeal lesions and defects is secondary to technologic advances in diagnosis and the development of sophisticated reconstructive techniques. Additionally, complicated laryngeal tumor resection and reconstruction require adequate and nonviolating access to lesions, allowing judicious tumor removal, and sparing of healthy tissues for reconstructive efforts.

The transverse infrahyoid approach for the removal of bilateral glottic tumors has proven to be relatively safe and highly effective. It provides superb tumor visualization and surgical access to bilateral vocal cord lesions, preserving the oncologic integrity of the procedure. Moreover, normal soft tissue and cartilage are preserved for laryngeal reconstruction. This approach is simple to perform, is easily incorporated into the operation without disruption or increased operating room time, and is not dependent upon the experience of perhaps a less-skilled surgeon for guidance. We have successfully employed the transverse infrahyoid approach in over 35 patients undergoing extensive glottic-level resections, without complication. Further, these procedures have never been compromised oncologically by inaccurate placement of incisions leading to positive resection margins. Accordingly, we recommend that this approach be employed in all patients with bilateral glottic tumors undergoing bilateral hemilaryngectomy procedures.

REFERENCES

1. Quinn HJ. Hemilaryngectomy. Indications and a standardized technique. South Med J 1969;62:1031-5.

2. Gluck W. Hemilaryngectomy. In: Kirschner M, Lautenschlager A, Kleinschmidt O, eds. Operative surgery: the ear, air passage and neck. Vol 3. Philadelphia, Pa: JB Lippincott, 1937:394-405.

3. Hautant A. Ma technique de l'hemilaryngectomie: ses resultats. Otorhinolaryngol Int 1930;5:217-24.

4. Som ML. Hemilaryngectomy: a modified technique for cordal carcinoma with extension posteriorly. Arch Otolaryngol 1951;54:524-30.

5. Kirchner JA, Som ML. Clinical significance of fixed vocal cord. Laryngoscope 1971;81:1029-44.

6. Biller HF, Ogura JH, Pratt LL. Hemilaryngectomy: for T-2 glottic cancers. Arch Otolaryngol 1971;93:238-43.

7. Zollinger WK, Alonso WA, Ogura JH. Perichondrial flap

reconstruction of the larynx. Trans Am Acad Ophthalmol Otolaryngol 1976;82:167-73.

8. Som ML, Arnold LM. Hemilaryngectomy: surgery for cordal carcinoma with extension posteriorly. In: Coates GM, Schenek HP, Miller M, eds. Otolaryngology. Vol 1. Hagerstown, Md: WF Prior, 1960:31-58.

9. Quinn HJ. Ten years' experience with free tissue grafts for glottic reconstruction. Trans Am Acad Ophthalmol Otolaryngol 1978;86:372-9.

10. Pressman JJ, Simon MB, Monell C. Anatomical studies related to the dissemination of cancer of the larynx. Trans Am Acad Ophthalmol Otolaryngol 1960;66:628-38.

11. Kirchner JA. One hundred laryngeal cancers studied by serial section. Ann Otol Rhinol Laryngol 1969;78:689-709.

12. Burns HB, Bryce DP, van Nostrand AWP. Conservation surgery in laryngeal cancer and its role following failed radiotherapy. Arch Otolaryngol 1979;105:234-9.

13. Pillsbury HRC, Kirchner JA. Clinical vs histopathologic staging in laryngeal cancer. Arch Otolaryngol 1979;105:157-9.

14. Kirchner JA. Two hundred laryngeal cancers: patterns of growth and spread as seen in serial section. Laryngoscope 1977;87:474-82.

15. McGavran MH, Spjut HJ, Ogura JH. Laryngofissure in the treatment of laryngeal carcinoma: a critical analysis of success and failure. Laryngoscope 1953;63:44-53.

16. Biller HF, Lawson W. Bilateral vertical partial laryngectomy for bilateral vocal cord carcinoma. Ann Otol Rhinol Laryngol 1981;90:489-91.

17. Kambic V. Epiglottoplasty. New technique for laryngeal reconstruction. Radiol Iugoslav 1977(suppl 2):33-43.

18. Sedlacek K. Application of the epiglottis as a pedunculated lobe in reconstructive surgery of the larynx. Otolaryngol Pol 1966;20:81-5.

19. Tucker HM, Wood BG, Levine HL, et al. Glottic reconstruction after near total laryngectomy. Laryngoscope 1977;87:609-18.

20. Kirchner JA, Som ML. The anterior commissure technique of partial laryngectomy: clinical and laboratory observations. Laryngoscope 1975;85:1308-17.

21. Reino AJ, Lee HY, Lawson W, Schaeffer-Mojica J, Biller HF. Management of bilateral glottic tumors. Arch Otolaryngol Head Neck Surg 1997;123:465-73.

22. Conley J. Regional skin flaps in partial laryngectomy. Laryngoscope 1975;85:942-9.

23. Conley J. The use of mucosal flaps for wound rehabilitation in partial laryngectomy. Arch Otolaryngol 1959;69:700-3.

24. Conley J. Glottic reconstruction and wound rehabilitation procedures in partial laryngectomy. Arch Otolaryngol 1961;74:239-42.

25. Conley JJ. Rehabilitation of the airway system by neck flaps. Ann Otol Rhinol Laryngol 1962;71:404-10.

26. Schechter GL. Conservation surgery of the larynx — when? Otolaryngol Clin North Am 1984;17:215-25.

27. Ogura JH, Biller HF. Glottic reconstruction following extended frontolateral hemilaryngectomy. Laryngoscope 1969;79:2181-4.

28. Mohr RM, Quenelle DJ, Shumrick DA. Vertico-frontolateral laryngectomy (hemilaryngectomy) indications, technique, and results. Arch Otolaryngol 1983;109:384-95.

29. Laccourreye H, Laccourreye O, Weinstein G, Menard M, Brasnu D. Supracricoid laryngectomy with cricohyoidoepiglottopexy: a partial laryngeal procedure for glottic carcinoma. Ann Otol Rhinol Laryngol 1990;99:421-6.

30. Quinn HJ Jr. A new technique for glottic reconstruction after partial laryngectomy. Laryngoscope 1969;79:1980-2011.

31. Collins SL. A safe approach to extensive glottic-level resections prior to epiglottic laryngoplasty. Laryngoscope 1995;105:1361-4.

≈

FIFTH INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Fifth International Conference on Head and Neck Cancer will be held July 29–August 2, 2000, in San Francisco, California. For information, contact Concepts in Meetings & Events, Robin L. Wagner, President, 7819 Lloyd Ave, Pittsburgh, PA 15218-1941; telephone (412) 243-5156; fax (412) 243-5160; e-mail rlwa@med.pitt.edu.

Ann Otol Rhinol Laryngol 108:1999

IMMUNOLOGIC AND HISTOLOGIC OBSERVATIONS IN REOVIRUS-INDUCED OTITIS MEDIA IN THE MOUSE

ROBERT B. MEEK III, MD   BENJAMIN M. MCGREW, MD   CHRISTOPHER F. CUFF, PHD
ALBERT S. BERREBI, PHD   GEORGE A. SPIROU, PHD   STEPHEN J. WETMORE, MD
MORGANTOWN, WEST VIRGINIA

The goals of this study were to develop a mouse model for virally induced otitis media, and to study the immune response to infection. Intranasal inoculation of mice by reovirus was used to induce otitis media. Immunohistochemical evidence for the presence of reovirus in the nasopharynx, eustachian tubes, and middle ears and the amount of infiltrating B-cells and T-cells in those sites were serially evaluated by painlessly sacrificing animals over a 21-day period. Reovirus antigen was detected in the middle ear mucosa by day 4 in 75% of infected animals, and histologic evidence for otitis media was found in 54% of all infected animals. A significant increase in B-cells in the nasopharynx and eustachian tubes was noted 7 to 10 days following infection. The number of infiltrating T-cells did not vary significantly from that in the control animals at any of the sites. These results provide a basis for further investigations of the immune response in otitis media.

KEY WORDS — immunocytochemistry, immunology, otitis media, reovirus, viruses.

INTRODUCTION

Acute otitis media (AOM) and otitis media with effusion (OME) are both common diseases of childhood. Bacteria can be cultured from the majority of cases of AOM, but from only about one third of cases of OME. A meta-analysis of OME showed that only 14% of cases were improved with systemic antibiotics.[1] Viral upper respiratory tract infection (URI) frequently precedes AOM, and viruses are now more commonly detected in chronic OME, thanks to modern diagnostic techniques such as the polymerase chain reaction.[2-5] Viruses have been implicated as sole causative agents or as predisposing agents for bacterial infection in these diseases.[6-11] We have developed an animal model, utilizing the induction of a viral URI, to study the role of viruses in developing middle ear disease.

A common effect of middle ear infection is the production of an inflammatory response with development of submucosal edema that results in leukocytic infiltration and, ultimately, in accumulation of middle ear fluid.[12] Despite the relative lack of immunocompetent cells, glands, and capillaries in the middle ear,[13-16] the contribution of the immune response in generating otitis media (OM) has been revealed in animal models by immunologic challenge independent of infection[17-19] and by surgical blockade of the eustachian tube.[20-22] Increasingly, mice have been used to study OM, because their immune systems are well characterized and because of the commercial availability of immunologic probes.[13,14,18,19,21,23]

Because several different viruses, such as influenza virus, adenovirus, and respiratory syncytial virus, have been implicated as predisposing agents in the development of OME,[6,7,10,11] it seems plausible that the inflammatory response to infection, and not the particular virus, is a critical determinant for the development of OME. Thus, even a relatively mild viral infection could initiate or contribute to OME if a substantial inflammatory response is generated following infection. This line of reasoning led us to develop the hypothesis that a subclinical viral infection could initiate OME or contribute to the development of OME following secondary bacterial infection. To test this hypothesis, we examined the inflammatory response in mice given a URI with reovirus. Reovirus (respiratory enteric orphan virus) typically produces a mild infection in immunocompetent mice, but is capable of eliciting strong cellular and humoral responses by the mucosal and systemic immune systems, which have been studied extensively. Reovirus has been used to study viral pathogenesis in several models of infection, includ-

---

From the Departments of Otolaryngology–Head and Neck Surgery (Meek, McGrew, Berrebi, Spirou, Wetmore) and Microbiology and Immunology (Cuff), West Virginia University School of Medicine, Morgantown, West Virginia. This work was supported by the West Virginia University Foundation and grants AI34544 (C.F.C.), and DC02266 (A.S.B.) from the National Institutes of Health. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals,* and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of West Virginia University.

CORRESPONDENCE — Stephen J. Wetmore, MD, Dept of Otolaryngology–Head and Neck Surgery, PO Box 9200 Health Sciences Center, West Virginia University School of Medicine, Morgantown, WV 26506.

ing neonatal, immunodeficient, and immunocompetent mice.[24-26]

In this paper we provide evidence that reovirus URI can induce substantial pathologic changes in the nasopharynx, eustachian tubes, and middle ears. The results of these studies demonstrate a model that could be used to elucidate the relationship between virus-induced inflammation of the upper respiratory tract and the development of OME. Understanding this relationship will help delineate molecular mechanisms of the pathogenesis of OME and, hopefully, provide molecular targets for intervention.

MATERIALS AND METHODS

Animals. Specific pathogen–free female Balb/c mice (Charles River, Wilmington, Mass) were used at 8 to 12 weeks of age. All mice were housed in specific pathogen–free conditions. Virus-infected mice were housed in a laminar flow hood in a separate room in the West Virginia University Health Science Center vivarium.

Virus Purification. Third-passage stocks of reovirus serotype 1, strain Lang, were grown in L929 cells at 34°C in a spinner flask in modified Eagle's medium (Whittaker Bioproducts, Walkersville, Md) supplemented with 5% fetal bovine serum (Hyclone, Ogden, Utah) and 2 mmol/L L-glutamine. Stocks of virus were purified by extraction with 1,1,2-trichloro-1,2,2 trifluoroethane (JT Baker, Phillipsburg, NJ) from L929 cell lysates, followed by discontinuous cesium chloride centrifugation at 200,000*g* for 3 hours. Titers of virus stocks were determined by plaque assay as previously described.[27] The purity of reovirus preparations was confirmed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. No bacterial contamination was detected following in vitro incubation of virus preparations in tissue culture or by visual inspection for turbidity.

Animal Infections. Mice were infected intranasally with 10^7 plaque-forming units of purified reovirus by means of a micropipette. Virus was diluted in borate-buffered saline containing 2% gelatin (gel saline) and administered in 2 successive doses of 20 μL per dose. Control animals were given sterile gel saline in a similar manner. Although virus is grown in low-endotoxin conditions, the sterile gel saline used as virus diluent and vehicle control contains endotoxin as determined by the limulus amebocyte lysate method (Pyrotell, Associates of Cape Cod, Inc, Woods Hole, Mass). Therefore, infected and vehicle-treated mice were exposed to essentially equivalent amounts of endotoxin. Groups of at least 3 animals per experiment were painlessly sacrificed on days 1, 2, 3, 4, 7, 10, 14, and 21 postinfection. On days 2, 4, 7, 10, and 14 — the days exhibiting the predominant pathologic changes — 10 to 12 animals were sacrificed on each day.

Serum Samples and Virus-Specific ELISA. Blood samples were collected at the time of perfusion. Serum was obtained by storing blood at 4°C for several hours, followed by centrifugation. Samples were assayed for reovirus-specific antibody by enzyme-linked immunosorbent assay (ELISA) as previously described.[28] Color development was read at 405 nm, and results are expressed as the serum antibody titers from individual mice. Titers were determined to be the last serum dilution that yielded an optical density of ≥0.200. Titration curves of known positive samples were linear from approximately 0.1 to 1.5 optical density units.

Histology. On the day of sacrifice, mice were anesthetized with 0.1 mL of ketamine hydrochloride (100 mg/mL) given intraperitoneally. Animals were perfused through the ascending aorta with 20 mL of saline, followed by 100 mL of 4% paraformaldehyde and 0.1% glutaraldehyde in 0.1 mol/L phosphate buffer (pH 7.3) prewarmed to 37°C. Heads were placed in Cal-ex decalcifying solution (Fisher Chemical Co, Fair Lawn, NJ) for 48 hours at 4°C, and subsequently dehydrated, embedded in paraffin at 60°C, and allowed to air-cool overnight. Axial sections of the heads were obtained at a thickness of 5 μm. Slides were stained with hematoxylin and eosin and were analyzed by light microscopy for pathologic changes in the epithelium and submucosa. To assess bacterial growth in the middle ear, Gram's stain was performed on 1 representative section from each infected animal that displayed histopathologic changes.

Immunohistochemistry. For immunohistochemistry, tissue sections were deparaffinized, rehydrated, and rinsed in phosphate-buffered saline (PBS). To enhance the immunoreactivity of the tissue sections, antigen retrieval was performed by incubating slides in a citric acid buffer containing 8 mmol/L sodium citrate and 2 mmol/L citric acid for 20 minutes in a steam chamber (Biogenex, San Ramon, Calif). Endogenous peroxidase activity was blocked by incubating slides in 3% hydrogen peroxide in PBS for 15 minutes. To inhibit nonspecific binding of primary antibodies and permeabilize the tissues, tissue sections were incubated in 5% normal donkey serum with 1% Triton-X for 30 minutes in PBS. Tissue sections were rinsed in PBS and exposed to primary antisera for 1 hour at room temperature. Slides were incubated in either rat anti-mouse B-220, which recognizes cells of the B-cell lineage (diluted 1:800; Pharmingen, San Diego, Calif), rat anti-mouse Thy-1, which recognizes cells of the T-cell lineage (diluted

TABLE 1. SERUM ANTIBODY RESPONSES IN REOVIRUS-INFECTED MICE

*Days Postinfection**	*n*	*Geometric Mean Titers†*
2	3	<200
7	6	2,015
10	5	>3,200
14	7	>3,200
21	5	>3,200

*Mice were infected intranasally with 10^7 plaque-forming units of reovirus, and virus-specific serum antibody titers were assessed by enzyme-linked immunosorbent assay.

†End points are defined as last dilution to yield optical density of ≥0.200.

1:200; Pharmingen), or rabbit anti-reovirus antiserum (diluted 1:1,000; Biogenesis, Sandown, NH). Sections were then rinsed in PBS, incubated in biotinylated secondary antibody for 30 minutes, rinsed again in PBS, and processed with the Vectastain Elite ABC kit (Vector Laboratories Inc, Burlingame, Calif) for 30 minutes as per the manufacturer's directions. Color reactions were developed with 3,3' diaminobenzidine tetrahydrochloride (DAB; Research Genetics, Huntsville, Ala), and a subset of sections were counterstained with light Gill's No. 3 hematoxylin (Biotek, Santa Barbara, Calif).

The intensity of immunostaining in T-cell and B-cell areas in spleen, mesenteric lymph node, and small intestine was examined to determine the appropriate dilutions of anti-lymphocyte antibodies. Titration of anti-reovirus antibody was determined by judging the immunostaining intensity of virus-infected and noninfected L-cells. Negative controls, obtained by omission of primary antiserum, failed to specifically stain any tissue (not shown).

Analysis. Pathologic findings in the middle ear submucosa and epithelia were assessed, and the thickness of the submucosa was measured at a location 500 µm lateral to the tympanic orifice of the eustachian tube, corresponding to the transition zone between ciliated columnar and simple squamous epithelia. Edema was defined as a submucosal thickness of 20 µm, corresponding to approximately 2 standard deviations above the mean thickness of control ears. The contents of the middle ear space were examined for evidence of middle ear cells (ie, leukocytes), debris (essentially acellular), and bacteria. The total numbers of immunopositive B-cells, T-cells, and macrophages were counted in 500-µm lengths of intraepithelial and submucosal tissue lining the middle ears, eustachian tubes, and nasopharynx. Data are expressed as the average number of cells per 500-µm length of tissue per mouse. Reovirus-specific staining was qualitatively assessed by examining the total intact epithelial lining of the nasopharynx, eustachian tubes, and middle ears for cytoplasmic immunostaining of reovirus antigen.

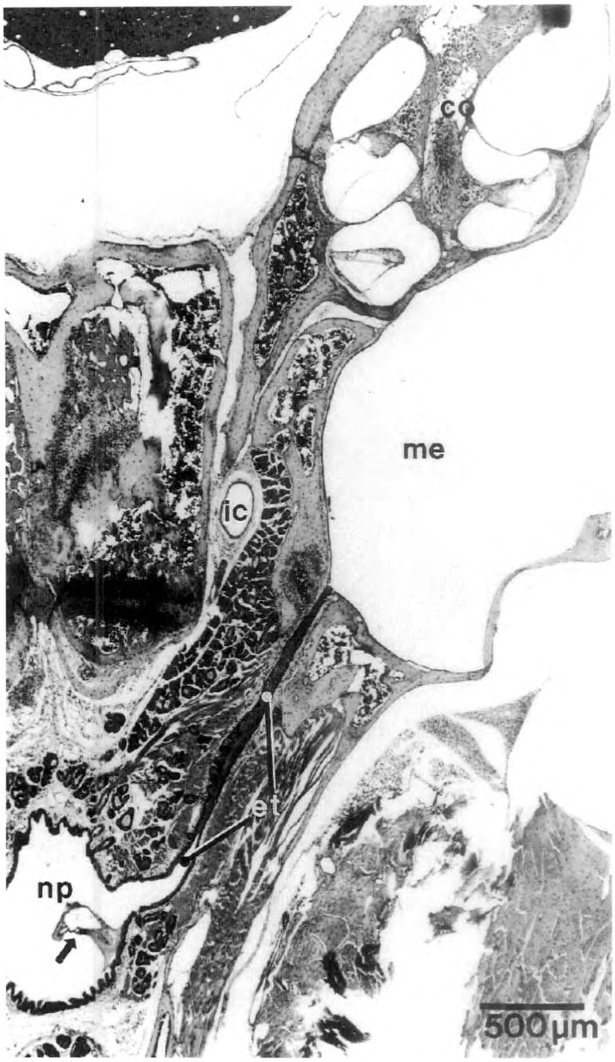


Fig 1. Axial section of head of control mouse (H & E). Caudal is to top of field; medial is to left. Eustachian tube (et) is sectioned longitudinally, with lumen of tube visible near nasopharynx (np). Note presence of mucus in nasopharynx (arrow), which is normal finding in infected and noninfected animals. Middle ear (me) is free of debris, and epithelium does not display inflammation. ic — internal carotid artery, co — cochlea.

Statistical Analyses. Data from the nasopharynx were analyzed with a 2-way analysis of variance (ANOVA) and Duncan's post hoc analysis. The bilateral eustachian tubes and middle ear tissues were analyzed by a 2-way repeated-measures ANOVA with Sigma Stat analysis software (San Rafael, Calif). A p value of <.05 was considered statistically significant.

RESULTS

Systemic Immune Response to Intranasal Virus Infection. All the infected mice underwent seroconversion and developed serum antibody titers of

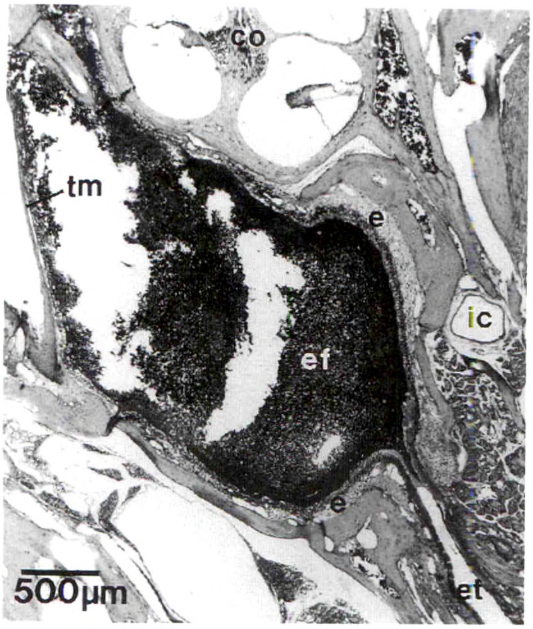


Fig 2. Middle ear and eustachian tube (et) at day 10 post–reovirus infection. Middle ear contains cellular effusion (ef) and exhibits submucosal edema (e). co — cochlea, ic — internal carotid artery, tm — tympanic membrane.

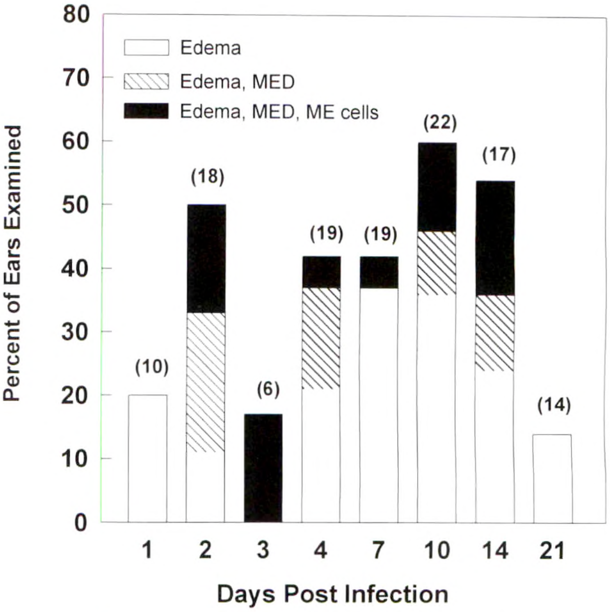


Fig 3. Summary of incidence of middle ear (ME) pathologic findings in reovirus-infected mice. At various days after infection, H & E–stained sections of ME were examined for presence of edema (white bars); edema with middle ear debris (MED; hatched bars); or edema, MED, and cellular effusions (dark bars). Numbers above bars indicate total number of ears examined at each time point. Peak in reovirus-induced middle ear pathologic findings is evident between 4 and 14 days postinfection.

>3,200 by 10 to 14 days after infection (Table 1). High antibody titers were observed through day 21. Serum samples from noninfected mice were antibody-negative by ELISA.

Reovirus-Induced Pathologic Changes in Middle Ears. Hematoxylin and eosin–stained sections from a total of 125 ears from 71 mice were examined. In axial sections, the nasopharynx, eustachian tube, and middle ear could be viewed simultaneously in the mouse. A representative section from a control mouse showing the middle ear, eustachian tube, and nasopharynx is provided in Fig 1.

Pathologic features in infected mice included the presence of middle ear edema, debris, and inflammatory cells in the middle ear space. Some or all of these characteristics were observed in a total of 42% (52/125) of the infected ears and 54% of the infected animals (38/71) and were most apparent 4 to 14 days after infection. An example of one of the most serious cases is shown in Fig 2. This type of result was observed in 8% (10/125) of ears examined. Maximal pathologic changes were observed at 10 days postinfection. Edema was the most common pathologic change, observed in 56% or 29 of 52 of the infected ears, followed in frequency by the appearance of middle ear debris and cellular middle ear effusions, each occurring in approximately 23% of the infected ears. There was also an early acute inflammatory response at 2 days postinfection that receded somewhat on days 3 to 7 (Fig 3). No sections from the infected middle ears contained bacteria by Gram's stain (data not shown). Infected mice displayed no signs of disease, such as ruffling of the fur or lethargy.

Control mice that received gel saline intranasally did not exhibit cellular effusions or inflammatory infiltrate. Mild edema was observed in only 1 of 18 ears from control mice.

Thickness of Epithelia and Submucosa. The epithelia and submucosa of control mice had a mean thickness of 11.5 µm (Table 2). Ears identified as edematous had an average measured thickness that was nearly fivefold greater than the thickness of nonedematous or control ears (Fig 4).

Immunohistochemical Analysis of Inflammatory Cells Following Infection. The inflammatory cell response in the epithelium was analyzed by immunohistochemical staining of fixed tissue sections. The number of cells bearing the B-cell marker B220 was increased following infection, particularly in the nasopharynx (Fig 5). A significant increase in the number of B220$^+$ cells was observed in the nasopharynx at 7 and 10 days postinfection, and in the eustachian tubes at 10 days postinfection (Fig 6). A slight increase in the number of B220$^+$ cells was found in the middle ears of infected mice at 14 days postinfection, but this increase was not statistically significant. An examination of Thy-1 staining in sections

TABLE 2. MIDDLE EAR EDEMA IN REOVIRUS-INFECTED MICE

Group	*No. of Ears Examined*	*Mean Submucosal Thickness*[a] *± SE (μm)*
Noninfected[b]		
Edematous	1	23.0
Nonedematous	17	10.8 ± <1
Reovirus-infected[c]		
Edematous	52	49.2 ± 6.7[d]
Nonedematous	73	9.2 ± <1

[a] Submucosal thickness was measured 500 μm from opening of eustachian tube.

[b] Mice were given 40 μL of gel saline intranasally and painlessly sacrificed 1 to 14 days later.

[c] Mice were infected with 10^7 plaque-forming units of reovirus in 40 μL of gel saline as described in Materials and Methods, and sacrificed 1 to 21 days later.

[d] Significantly different from controls (18 ears, 11.5 ± 1.0 μm) and nonedematous ears by analysis of variance.

from the same mice revealed no statistically significant increase in the number of T-cells in the epithelia of infected mice between 1 and 21 days postinfection (data not shown).

Detection of Viral Antigen in Infected Mice. The extent of viral spread from the nasopharynx, the initial site of infection, was analyzed by staining sections with polyclonal anti-reovirus antiserum. Cytoplasmic staining for reovirus antigen was detected in the epithelial cells of the nasopharynx of all infected animals between 1 and 14 days postinfection, but became undetectable by day 21 postinfection. Epithelial cells of the eustachian tubes were immunopositive at days 3 and 4 postinfection in 7 of 8 mice. Reovirus antigen was found to be most prevalent in the middle ear on days 3 and 4 (Fig 7), when it was detected in the mucosa of 8 of 14 ears, but it could not be detected at day 14 postinfection.

DISCUSSION

This model of viral OM illustrates the common scenario of a URI preceding an episode of acute OM and shows a direct connection between viral infection, the development of a local inflammatory response, and the production of OM. Reovirus consistently gave rise to a URI, as indicated by histopathologic changes within the nasopharynx, and led to the development of OM. Previous viral models of OM in the chinchilla produced a lower incidence of OM following intranasal inoculation of influenza A and adenovirus without concomitant bacterial challenge.[7,9,10]

As with other methods of inducing OM in chinchillas and mice, reovirus infection produced an initial inflammatory response consisting primarily of neutrophils and the development of submucosal edema. The initial appearance of middle ear pathologic findings on day 2 postinfection is most likely mediated by the innate immune response to reovirus infection, since at this early time point, obstruction- and negative pressure–induced transudation of serum into the middle ear is unlikely.

Infected mice mounted a systemic immune response to the reovirus inoculation, as evidenced by seroconversion that occurred by day 7 postinfection. Seroconversion preceded the maximal histopathology observed at day 10 postinfection, consistent with previous findings of immune complex–mediated

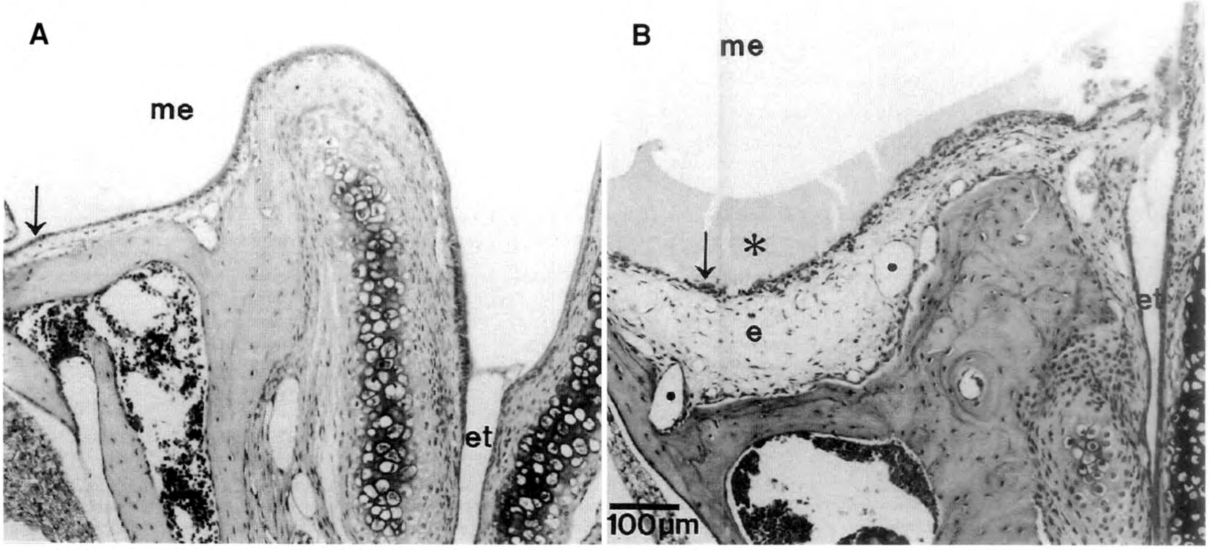


Fig 4. Photomicrographs of middle ear (me) and eustachian tube (et) from A) control mouse and B) infected mouse. Arrows mark location where measurements of edema were made. Note presence of significant edema (e), dilated capillaries (dots), and overlying debris (asterisk) in reovirus-infected ear.

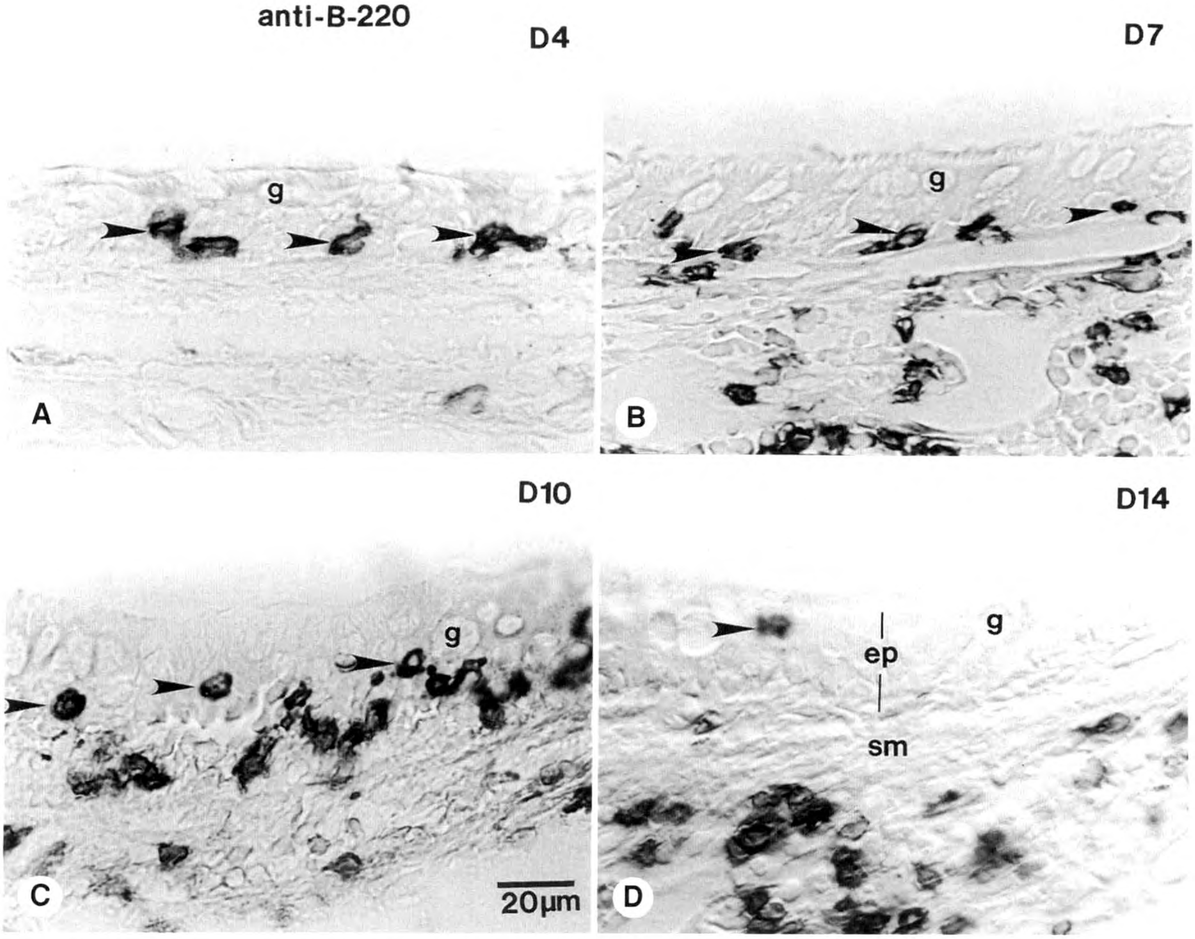


Fig 5. B220-immunoreactive B-cells (arrowheads) in epithelium of nasopharynx. Epithelium (ep) and submucosa (sm) are shown on A) day 4, B) day 7, C) day 10, and D) day 14 postinfection. Nomarski interference optics were used to photograph these sections to improve visualization of immunonegative tissue components. Control animals showed no specific immunostaining of these tissues. g — goblet cells.

OME.[17,18,29-32] A lymphocytic response consisting of B220+ cells was found in the nasopharynx, arising between day 4 and day 7 postinfection. Maximal numbers of B220+ cells were found in both the nasopharynx and eustachian tube on day 10, corresponding to the greatest extent of middle ear pathologic changes. The number of B220+ cells within the middle ear submucosa did not differ significantly from control levels at any time point, but an upward trend was noted from days 7 to 14 postinfection and might have become statistically significant given a larger sample size. However, even in the absence of a local B-cell infiltration, middle ear histopathologic changes may have been mediated by reovirus-specific antibody produced elsewhere and entering the middle ear by transudation.[31]

Thy-1–expressing lymphocytes were less numerous than B220+ cells, and interestingly, their frequency did not differ significantly from that in control animals in the nasopharynx, eustachian tube, or middle ear. Previous studies using animal models of OM have examined the issue of whether OM is an immune complex disease mediated by antibody, or a delayed-type hypersensitivity disease mediated by T-cells. Ryan et al[17] described a pathologic picture that resembled immune complex disease in keyhole limpet hemocyanin–immune guinea pigs. In contrast, Ichimiya et al[18] described OM that resembled a T-cell–mediated disease in dinitrophenyl-ovalbumin–treated C3H mice. We originally hypothesized that if pathologic findings developed in reovirus-infected mice, they would more closely resemble a T-cell–mediated disease, since immunity to viruses requires a potent T-cell response. In contrast, our findings suggest that the inflammatory response more closely resembles a B-cell–mediated reaction, because we found an increased number of B220+ cells in the epithelium following infection. C3H mice are known to mount immune responses that result in the development of strong T-cell–mediated immunity.[28,33] It is possible, therefore, that differences in the pathologic picture among these models are due in part to the strain and species of animal tested. It would be

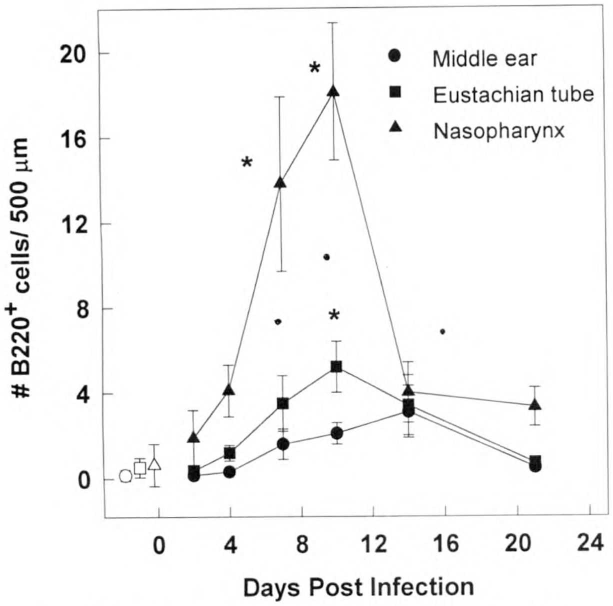


Fig 6. Reovirus infection resulted in increase in B220-immunopositive cells in nasopharynx, eustachian tube, and middle ear. Closed symbols represent average (± SEM) from 3 to 5 infected animals per time point. Open symbols represent average (± SEM) of control animals. Comparisons of counts from infected and control animals were made at each time point. Asterisks — significant group differences.

informative to examine the response to reovirus infection in C3H or B-cell–deficient mice to evaluate the contribution of the cell-mediated immune response in the absence of humoral immunity. These results most likely indicate that virus-specific T-cell responses are expressed in the draining lymph nodes or spleen and that T-cells do not migrate to the eustachian tube or middle ear in response to infection.

Reovirus antigen was detected in the eustachian tube and middle ear mucosa of infected animals as early as day 3 postinfection, and in most animals by day 4 postinfection. These animals were housed in specific pathogen–free conditions and exhibited no evidence of middle ear bacterial contamination by Gram's stain of the tissue. Thus, OM was most likely induced by direct viral cytolysis and the production of a local inflammatory response in the middle ear. Although we cannot exclude eustachian tube obstruction due to edema and lymphocytic infiltrate as a cause of OM, we show that reovirus does infect the middle ear mucosa at an early stage and most likely initiates the production of inflammatory mediators within the middle ear.

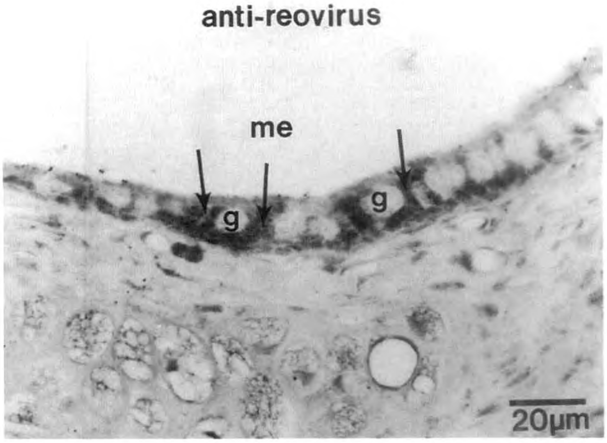


Fig 7. Reovirus antigen immunostaining (arrows) in middle ear (me) mucosa on day 4 postinfection. Dark immunoreactivity was observed within cytoplasm (arrows) of epithelial cells. g — goblet cells.

This animal model of reovirus infection is relevant because reoviruses are ubiquitous in nature and infect essentially all mammalian species, including humans and mice. Although reoviruses are orphan viruses, compelling serologic evidence exists that humans become infected early in life.[27,34,35] In addition, reovirus has been implicated as a possible etiologic agent for the common cold, but produces a mild or asymptomatic infection in healthy individuals.[36] Taken together, these studies in humans suggest that reovirus infection commonly occurs, especially in children, and that the clinical effects of primary infection typically go unrecognized. Whether reovirus infection induces pathologic changes in the upper respiratory tract in humans is not known; however, in rodents, reovirus infection produces a lower respiratory tract infection with significant pathologic findings.[37] Further, reovirus infection has been shown to reduce clearance of bacterial infection in the lung, mimicking the clinical picture of secondary bacterial infection following viral pneumonia.[38] Whether reovirus is an etiologic agent of OM in humans is not addressed by this study. Rather, we report that a mild URI induced by a respiratory virus well documented to naturally infect humans and mice can generate a pathologic picture consistent with OM. This model of OM in the mouse should shed further light on the interaction of viral URIs and the immune system, and provide a basis for identifying the specific components of the innate and adaptive immune responses, such as cytokines, that are involved in OM.

ACKNOWLEDGMENTS — We gratefully acknowledge the expert technical assistance of Sharlene Miranov, Mary Chesney, Michelle McCormick, Brenda Ford, and Shari Duvall.

REFERENCES

1. Stool SE, Berg AO, Berman S, et al. Otitis media with effusion in young children. Clinical Practice Guideline. 12th ed. Rockville, Md: Agency for Health Care Policy Research, Public Health Service, US Department of Health and Human

Services, 1994.

2. Ruuskanen O, Arola M, Putto-Laurila A, et al. Acute otitis media and respiratory virus infections. Pediatr Infect Dis J 1989; 8:94-9.

3. Arola M, Ziegler T, Puhakka H, Lehtonen O-P, Ruuskanen O. Rhinovirus in otitis media with effusion. Ann Otol Rhinol Laryngol 1990;99:451-3.

4. Uhari M, Hietala J, Tuokko H. Risk of acute otitis media in relation to the viral etiology of infections in children. Clin Infect Dis 1995;20:521-4.

5. Shaw CB, Obermyer NE, Wetmore SJ, Spirou GA, Farr RW. The incidence of adenovirus and respiratory syncytial virus in chronic otitis media with effusion utilizing the polymerase chain reaction. Otolaryngol Head Neck Surg 1995;113:234-41.

6. Giebink GS, Ripley ML, Wright PF. Eustachian tube histopathology during experimental influenza A virus infection in the chinchilla. Ann Otol Rhinol Laryngol 1987;96:199-206.

7. Lim DJ, Ohashi Y, Chung MH, DeMaria TF. Animal model for influenza A otitis media. Pediatr Infect Dis J 1989; 8(suppl):S38-S40.

8. Suzuki K, Bakaletz LO. Synergistic effect of adenovirus type a and nontypeable *Haemophilus influenzae* in a chinchilla model of experimental otitis media. Infect Immun 1994;62: 1710-8.

9. Park K, Bakaletz LO, Coticchia JM, Lim DJ. Effect of influenza A virus on ciliary activity and dye transport function in the chinchilla eustachian tube. Ann Otol Rhinol Laryngol 1993;102:551-8.

10. Bakaletz LO, Daniels RL, Lim DJ. Modeling adenovirus type-1 induced otitis media in the chinchilla; effect on ciliary activity and fluid transport function of eustachian tube mucosal epithelium. J Infect Dis 1993;162:865-72.

11. Chung MH, Griffith SR, Park KH, Lim DJ, DeMaria TF. Cytological and histological changes in the middle ear after inoculation of influenza-A virus. Acta Otolaryngol (Stockh) 1993;113:81-7.

12. Wright CG, Meyerhoff WL. Pathology of otitis media. Ann Otol Rhinol Laryngol Suppl 1994;103(suppl 163):24-6.

13. Takahashi M, Harris JP. Anatomic distribution and localization of immunocompetent cells in normal mouse endolymphatic sac. Acta Otolaryngol (Stockh) 1988;106:409-16.

14. Takahashi M, Peppard J, Harris JP. Immunohistochemical study of murine middle ear and eustachian tube. Acta Otolaryngol (Stockh) 1989;107:97-103.

15. Ryan AF, Sharp PA, Harris JP. Lymphocyte circulation to the middle ear. Acta Otolaryngol (Stockh) 1990;109:278-87.

16. Bernstein JM. Immunologic reactivity in the middle ear in otitis media with effusion. Otolaryngol Clin North Am 1991; 24:845-57.

17. Ryan AF, Catanzaro A, Wasserman SI, Harris JP. Secondary immune response in the middle ear: immunological, morphological, and physiological observations. Ann Otol Rhinol Laryngol 1986;95:242-9.

18. Ichimiya I, Ueyama S, Mogi G. Experimental otitis media in mice. Acta Otolaryngol Suppl (Stockh) 1988(suppl 457): 148-53.

19. Krekorian TD, Keithley EM, Takahashi M, Fierer J, Harris JP. Endotoxin-induced otitis media with effusion in the mouse. Immunohistochemical observations. Acta Otolaryngol (Stockh) 1990;109:288-99.

20. Sakagami M, Harada T, Juhn SK, Duvall AJ III. Morphologic and biochemical study of vascular permeability of the middle ear mucosa in experimental otitis media. Ann Otol Rhinol Laryngol 1990;99:654-9.

21. Johnson MD, Contrino A, Contrino J, Maxwell K, Leonard G, Kreutzer D. Murine model of otitis media with effusion: immunohistochemical demonstration of IL-1*alpha* antigen expression. Laryngoscope 1994;104:1143-9.

22. Johnson MD, Fitzgerald JE, Leonard G, Burleson JA, Kreutzer DL. Cytokines in experimental otitis media with effusion. Laryngoscope 1994;104:191-6.

23. Krekorian TD, Keithley EM, Fierer J, Harris JP. Type B *Haemophilus influenzae*–induced otitis media in the mouse. Laryngoscope 1991;101:648-56..

24. Tyler KL, Fields BN. Reoviruses. In: Fields BN, Knipe DM, eds. Fields' virology. New York, NY: Raven Press, 1990: 1307-28.

25. Nibert ML, Furlong DB, Fields BN. Mechanisms of viral pathogenesis. Distinct forms of reoviruses and their roles during replication in cells and host. J Clin Invest 1991;88:727-34.

26. Barthold SW, Smith AL, Bhatt PN. Infectivity, disease patterns, and serologic profiles in reovirus serotypes 1, 2, and 3 in infant and weanling mice. Lab Anim Sci 1993;43:425-30.

27. Leers WD, Royce KR. A survey of reovirus antibodies in sera of urban children. Can Med Assoc J 1966;94:1040-2.

28. Major AS, Cuff CF. Effects of the route of infection on immunoglobulin G subclasses and specificity of the reovirus-specific humoral immune response. J Virol 1996;70:5968-74.

29. Suzuki M, Kawauchi H, Mogi G. Immune-mediated otitis media with effusion. Am J Otolaryngol 1988;9:199-209.

30. Tanaka T, Kurono Y, Kawauchi H, Mogi G. Effect of oxatomide on otitis media with effusion. An experimental study. Acta Otolaryngol (Stockh) 1995;115:532-8.

31. Bakaletz LO, Holmes KA. Evidence for transudation of specific antibody into the middle ears of parenterally immunized chinchillas after an upper respiratory tract infection with adenovirus. Clin Diagn Lab Immunol 1996;4:223-5.

32. Ueyama S, Yuichi K, Haruo S, Masashi S, Mogi G. The role of immune complex in otitis media with effusion. Auris Nasus Larynx 1997;24:247-54.

33. Scott P. IFN-gamma modulates the early development of Th1 and Th2 responses in a murine model of cutaneous leishmaniasis. J Immunol 1991;147:3149-55.

34. Lerner AM, Cherry JD, Klein JO, Finland M. Infections with reoviruses. N Engl J Med 1947;267:947-53.

35. Selb B, Weber B. A study of human reovirus IgG and IgA antibodies by ELISA and Western blot. J Virol Methods 1994;47:15-26.

36. Jackson GC, Muldoon RL, Cooper RS. Reovirus type 1 as an etiologic agent of the common cold [Abstract]. J Clin Invest 1961;40:1051.

37. Bellum SC, Hamamdzic D, Thompson AH, Harley RA, London SD, London L. Experimental reovirus serotype 1/strain Lang infection of the lung: a model for the study of the lung in the context of mucosal immunity. Lab Invest 1996;74:221-31.

38. Klein JO, Green GM, Tilles JG, Kass EH, Finland M. Effect of intranasal reovirus infection on antibacterial activity in the mouse lung. J Infect Dis 1969;119:43-50.

Ann Otol Rhinol Laryngol 108:1999

ENDOSCOPIC MIDDLE EAR SURGERY

MUAAZ TARABICHI, MD
DUBAI, UNITED ARAB EMIRATES

One hundred sixty-five middle ear procedures were performed with an endoscope, a camera, and a video monitor instead of the microscope. The endoscope offers the following advantages: 1) it visualizes the whole tympanic membrane and the ear canal without having to manipulate the patient's head or the microscope, 2) it extends the operative field in transcanal procedures into structures usually hidden from the microscope (anterior tympanic perforation, posterior retraction pocket, facial recess, and hypotympanum), and 3) it visualizes structures from multiple angles as opposed to the microscope's single axis along the ear canal. Disadvantages of the endoscope include the one-handed surgical technique, a loss of depth perception, limited magnification, and the need for training. The endoscope holds the greatest promise in tympanoplasty and cholesteatoma surgery and should increase the utilization of transcanal over postauricular procedures.

KEY WORDS — cholesteatoma, endoscope, middle ear surgery, operative endoscopy, tympanoplasty.

INTRODUCTION

Despite the increased awareness of the role of the endoscope in otology, it has been primarily used as a diagnostic instrument. Operative endoscopy has been limited to transmeatal exploration of old mastoid cavities and removal of limited disease.[1] Many of the advantages that make the endoscope a superior diagnostic instrument could be applied to operative otology. Over the last 5 years, I have increasingly relied on the endoscope for middle ear surgery, and it has replaced the microscope as the central instrument in my practice. This report describes experience with 165 middle ear procedures performed solely with the endoscope.

PROCEDURES

Over a 5-year period, 165 middle ear procedures were performed with an endoscope, a video camera, and a monitor. This included 96 tympanoplasties, 13 stapedectomies, 53 transcanal procedures for removal of acquired cholesteatoma, and 3 procedures for removal of congenital cholesteatoma from the middle ear. All surgical tasks were performed with the endoscope and minor modifications of established surgical approaches and techniques. This experience was preceded by 3 years of gradual adaptation of endoscopic techniques to replace microscopic surgery.

INSTRUMENTATION

I used primarily the 4-mm wide angle (20 cm length) 0° and 30° sinuscopes. Other, smaller-diameter scopes were used sparingly.

The video equipment consisted of a 3-chip video

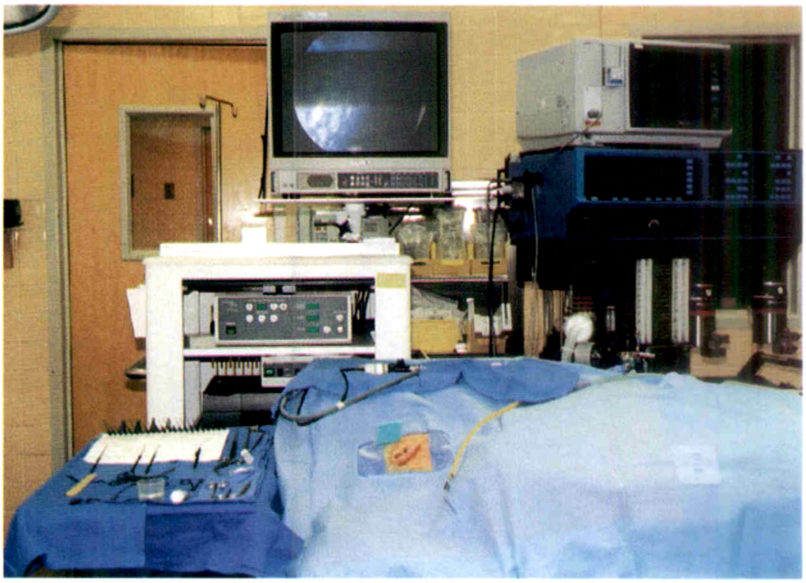


Fig 1. Operating room setup for endoscopic ear surgery.

From the Section of Otolaryngology, American Hospital–Dubai, Dubai, United Arab Emirates.

CORRESPONDENCE — Muaaz Tarabichi, MD, Section of Otolaryngology, American Hospital–Dubai, PO Box 5566, Dubai, United Arab Emirates.

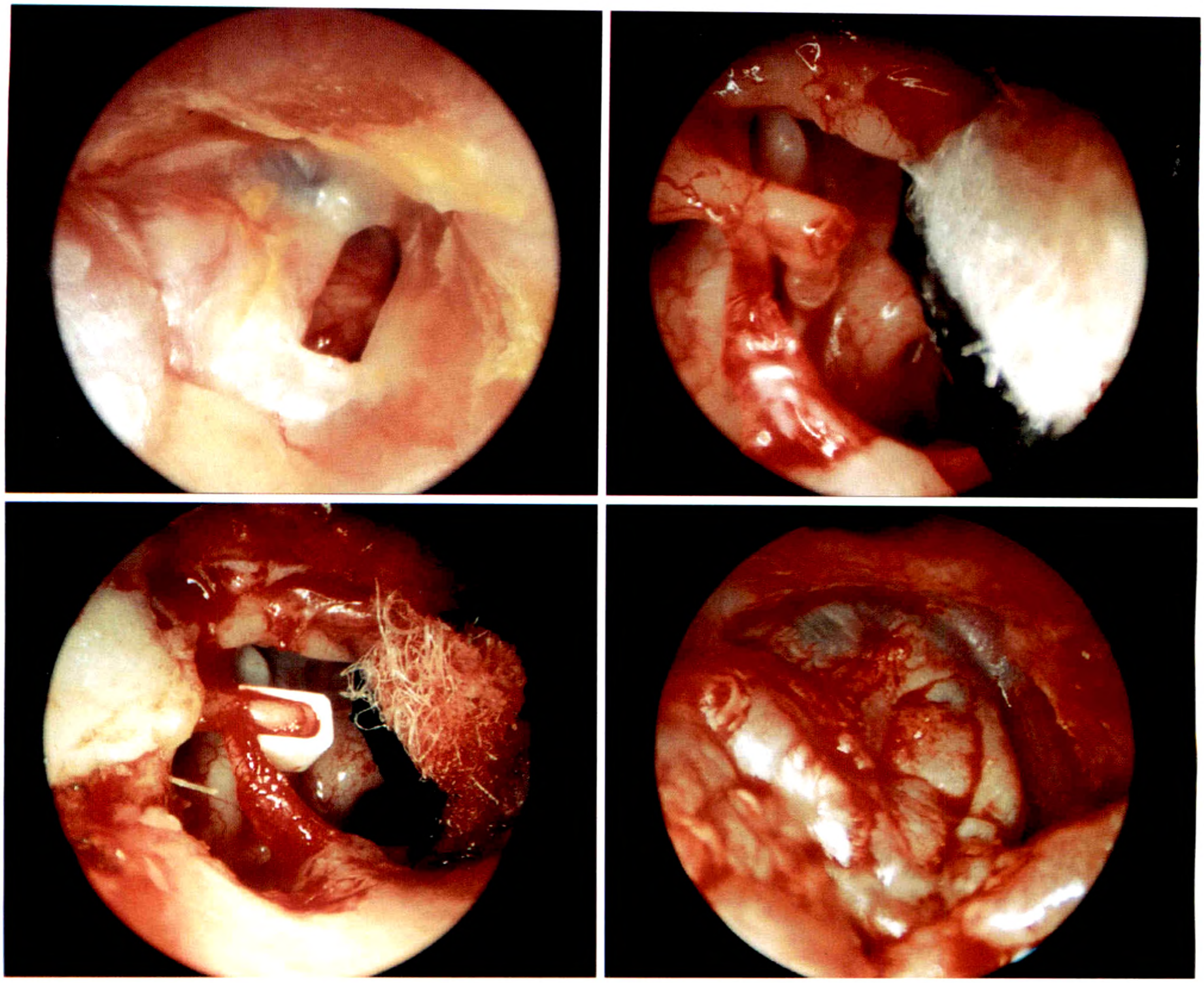


Fig 2. Right ear of 45-year-old male patient. Top left — preoperative endoscopic examination of tympanic membrane. Top right — dislocation of incudostapedial joint. Note that chorda tympani nerve is medial to incus. Bottom left — Applebaum prosthesis in position. Bottom right — endoscopic examination after repositioning of tympanomeatal flap.

camera and a monitor. All of the procedures were performed directly off the monitor and were recorded.

Initially, most picks, elevators, and curettes were modified with a 20° deflection at 1 cm from the tip of the instrument. In the last year, I have used Otoview instruments (Smith & Nephew Richards, Memphis, Tenn) in conjunction with routine microscopic ear surgery instruments.

The monitor was placed on the other side of the table, across the patient's head (Fig 1). A Mayo stand was used to hold up the camera and to hold the scope clear of the patient's head. (Most of these procedures were done under local anesthesia.) An absorbent pad soaked with antifog solution was pasted on the drapes above the patient's ear (Fig 1).

CASE REPORTS

A 45-year-old man was involved in a motor vehicle accident, resulting in multiple facial fractures and bleeding from the right ear. He was evaluated 3 months later and was found to have perforation of the tympanic membrane with no evidence of infection (Fig 2). An audiogram showed a substantial conductive hearing loss (Fig 3A). Under local anesthesia, the middle ear was explored and dislocation of the incudostapedial joint was identified (Fig 2). An Applebaum prosthesis was positioned, and a fascial graft was used to close the perforation (Fig 2). Follow-up at 2 months showed closure of the perforation, and an audiogram showed complete closure of the air-bone gap (Fig 3B).

A 52-year-old man had persistent anterior tympanic membrane perforation on the left side (Figs 4 and 5). Transcanal endoscopic lateral graft tympanoplasty was performed (Figs 6 and 7). Endoscopic examination performed 1 year postoperatively showed closure of the perforation (Fig 8).

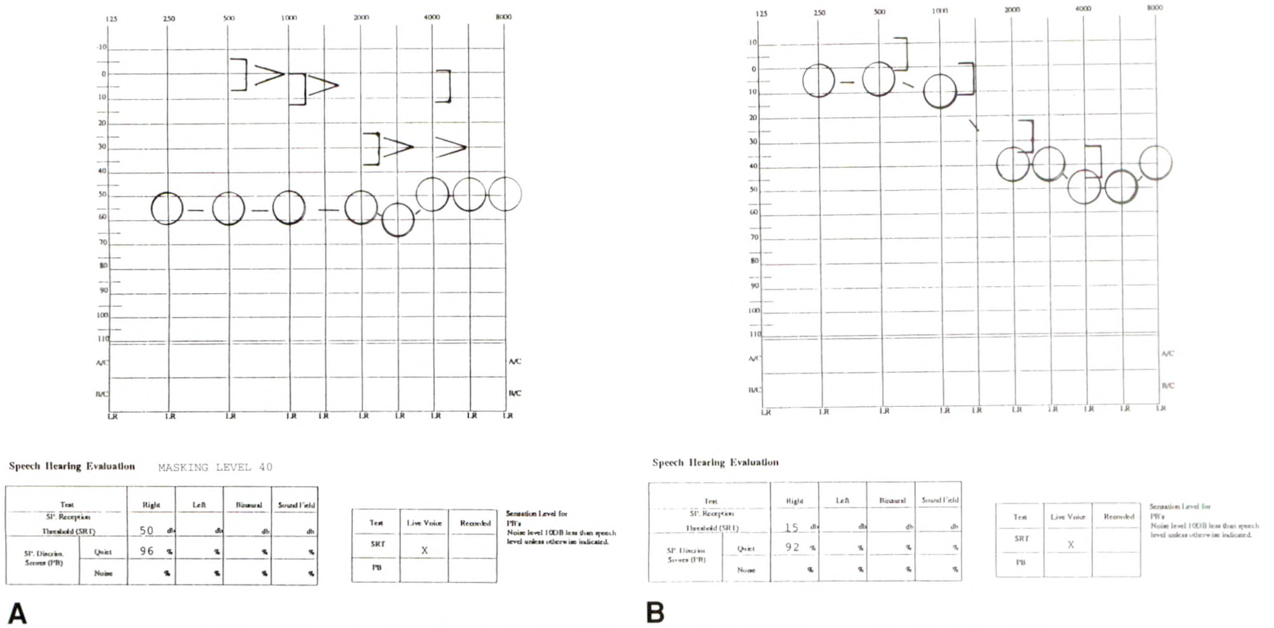


Fig 3. Audiograms of patient in Fig 2. A) Preoperatively. B) Two months postoperatively.

A 3-year-old child with congenital cholesteatoma in the anterior part of the right middle ear underwent transcanal removal via a superiorly based tympanomeatal flap (Fig 9).

RESULTS

Since the nursing staff was very familiar with endoscopic sinonasal procedures, the setup time for instruments and video equipment was comparable to that of microscopic ear surgery. The operative time was likewise comparable with that of microscopic surgery. The postauricular approach was utilized in only 3 of 53 procedures performed for acquired cholesteatoma. All tympanoplasty patients had transcanal procedures, even in the presence of an anterior overhanging ear canal and/or anterior perforation. There were no untoward intraoperative events. The size of the ear canal was not a limiting factor, even in the 2 patients in the group who were younger than 5 years old. None of the patients had worsening of sensorineural hearing loss (defined as >10 dB change in bone conduction thresholds at 0.5, 1, 2, or 3 kHz), except for 1 patient who had 15-dB worsening of bone conduction at 3 kHz. This particular patient had presented with severe sensorineural hearing loss and dizziness that lasted for 1 week prior to initial evaluation. The patient did have a lateral semicircular canal fistula. There were no reports of intraoperative dizziness by patients under local anesthesia. There were no iatrogenic facial nerve injuries in this series. The Table shows a summary of the different procedures performed and their outcomes. This is intended as a brief overview of the early results and is not presented as evidence of the superiority of endoscopic techniques over traditional methods. How-

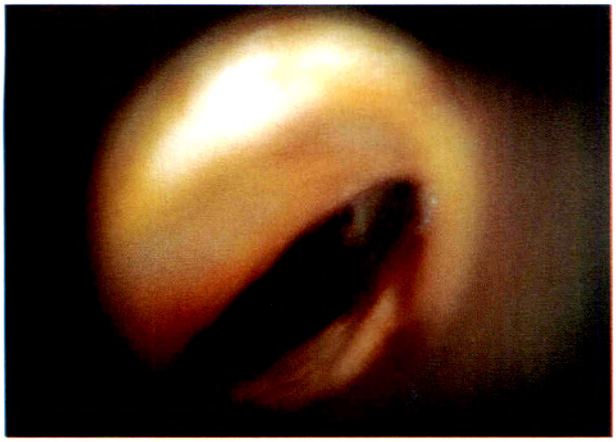


Fig 4. Left ear of 52-year-old man. Microscopic view of anterior perforation.

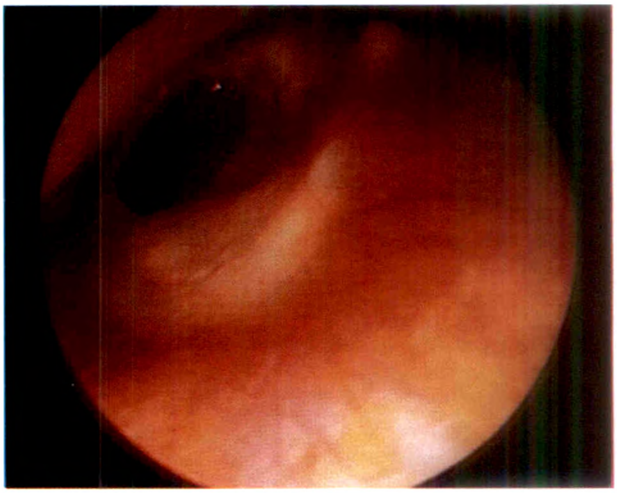


Fig 5. Endoscopic view of same perforation seen in Fig 4.

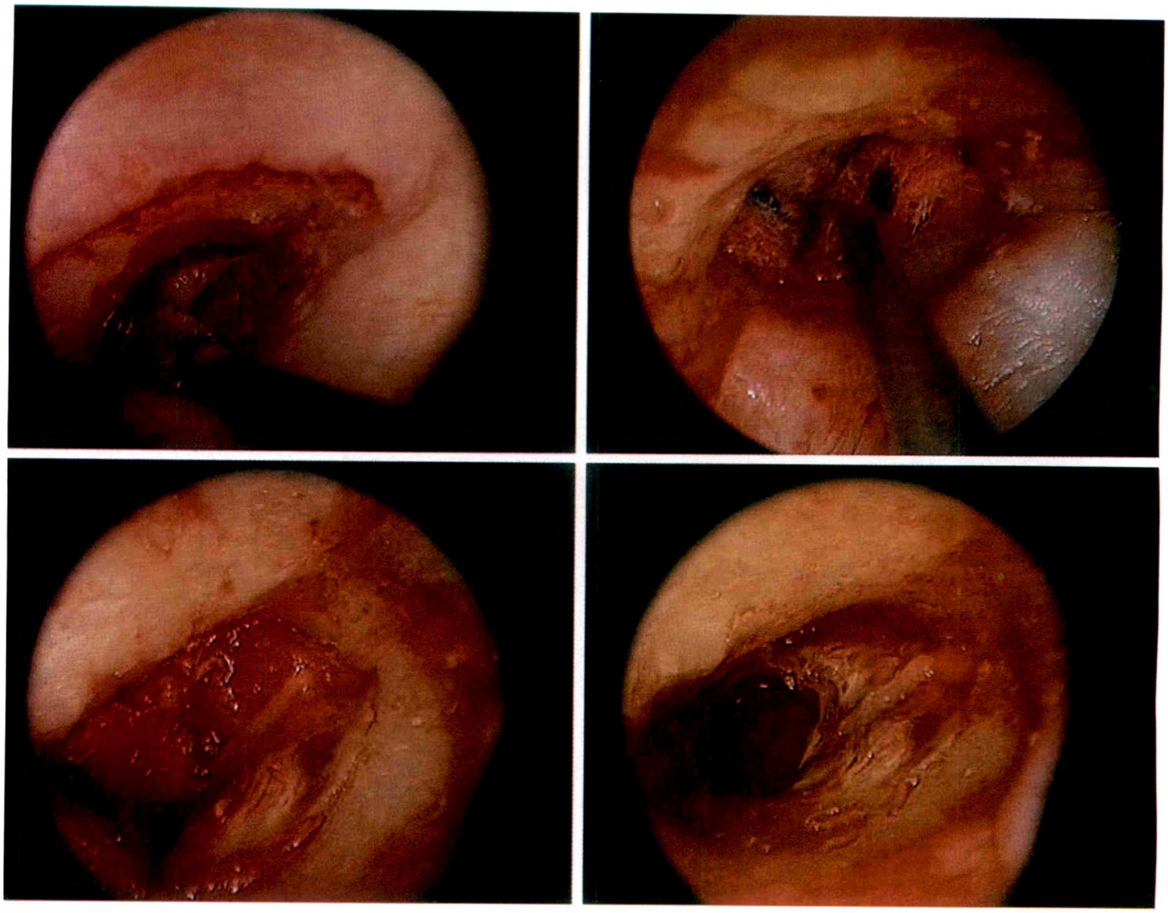


Fig 6. Endoscopic transcanal lateral graft tympanoplasty of left ear in Fig 4. Top left — removal of canal skin. Top right — vascular strip preserved. Bottom left and right — de-epithelialization of tympanic membrane.

ever, the results of endoscopic lateral graft tympanoplasty compare favorably with results cited in the literature.[2] Endoscopic medial graft tympanoplasty compared favorably with a historical group of 50 consecutive microscopic procedures performed previously with the endoscope by the same surgeon, with 88% of ears showing closure of perforation.

DISCUSSION

The introduction of the binocular operating microscope was a landmark event in the development of modern otology, and it clearly changed the scope and character of ear surgery. Despite continuous technical improvements, the basic optical principles, and their limitations, have stayed the same over the last 3 decades. With the introduction of the endoscope into other branches of surgery, there have been attempts at its utilization in otology. The diagnostic — mostly photographic — role of the endoscope for examining the tympanic membrane and the ear canal has been widely publicized.[3] Transtympanic middle ear endoscopy was initially reported by Nomura[4] and Takahashi et al.[5] Poe and Bottrill[6] described transtympanic endoscopy for the confirmation of perilymphatic fistula, as well as the identification of other middle ear disorders. McKennan[7] described second-look endoscopic inspection of mastoid cavities through a small postauricular incision. Thomassin et al[1] reported operative ear endoscopy for mastoid cavities and designed an instrument set to be used in these settings. Other investigators looked at the role of the endoscope in neurotologic procedures.[8]

The need for magnification in otologic surgery and the small diameter of the ear canal necessitate a careful consideration of the optical and physical properties of the different rigid endoscopes. It is helpful to review the basic types and functional properties of the rigid endoscopes.[9]

The Achromat lens scope utilizes serial thin lenses to relay the image. It is commonly used when a larger scope is applicable.

The rod lens scope, first developed by Hopkins, uses rod-shaped glass lenses in the relay system. The lenses are thick and the air spaces are small. The rod lens provides for a wider viewing angle and exceptional resolution and brightness. Most sinus endoscopes and smaller endoscopes belong in this category.

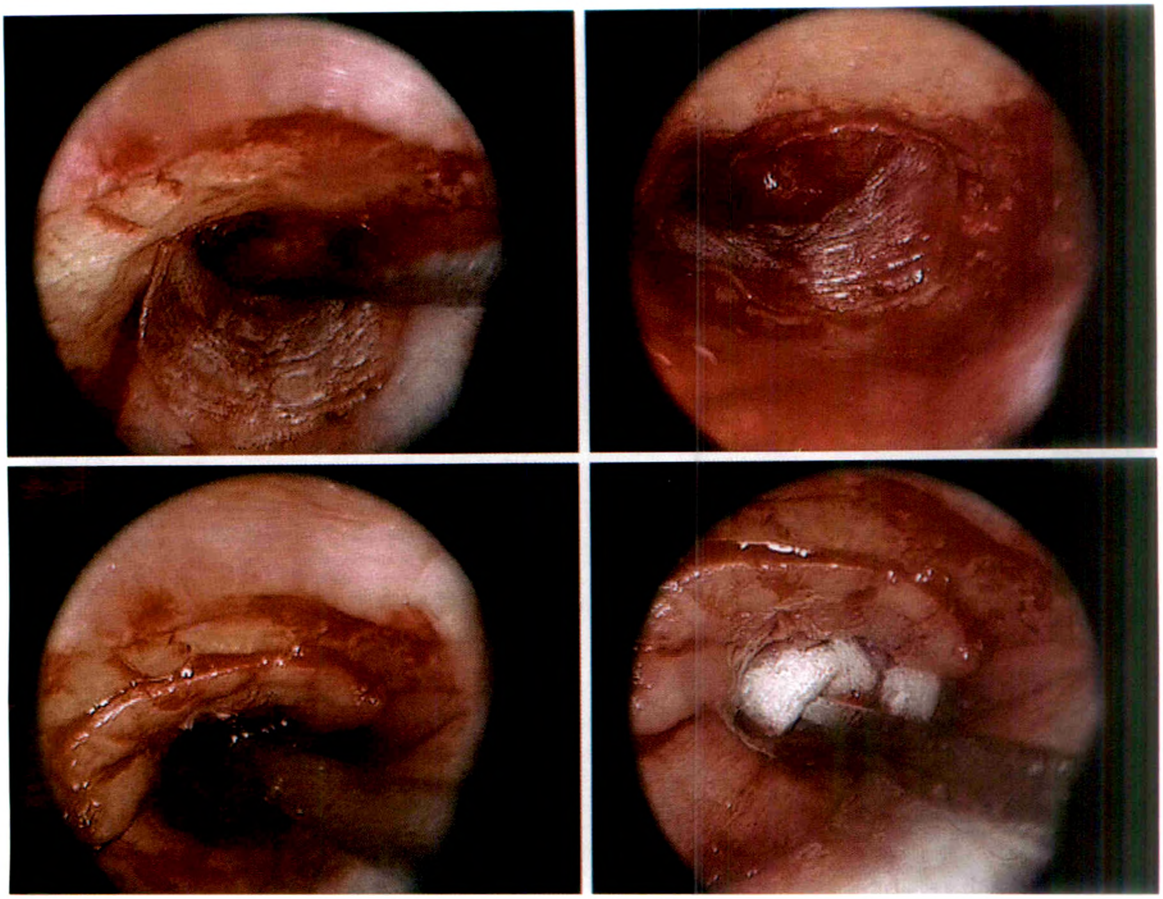


Fig 7. Endoscopic transcanal lateral tympanoplasty of left ear in Fig 4. Top left — graft introduced into canal. Top right — graft in position. Bottom left — canal skin repositioned. Bottom right — Gelfoam packing applied.

The Selfoc scope has reduced image quality, but is a more durable and cheaper scope when compared with the rod and Achromat lens scopes.

Basic definitions of terms used in endoscopy include the following.

"Length" or "functional length" does not include the handle or the eyepiece. Shorter endoscopes, less than 16 cm, are difficult to use in otologic procedures, because the bulky eyepiece and camera are too close to the ear and are within the range of movement of the hand holding the operating instruments. Smaller-diameter endoscopes have a very limited field of view and do not provide much advantage over the limited angle of view of the microscope. The 4-mm diameter of the scope has not been a limiting factor, even in small ear canals. The endoscope is usually removed and reintroduced when the surgical instrument is changed.

"Direction of view" is the angle between the mechanical axis and the center of the field of view.

"Field of view" is the angle measured at the tip of the endoscope to 2 points at the extreme diameter of the viewed field. This tends to increase substantially with the diameter of the endoscope; hence, it is advantageous to use the largest-diameter endoscope possible.

"Depth of field" is the distance between an object placed as close as possible to the distal tip of the scope while remaining in focus (near object distance)

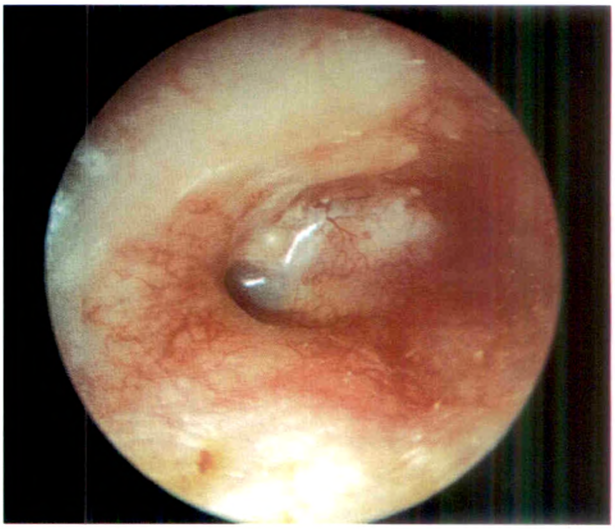


Fig 8. Endoscopic view at 1 year postoperatively of left ear in Fig 4.

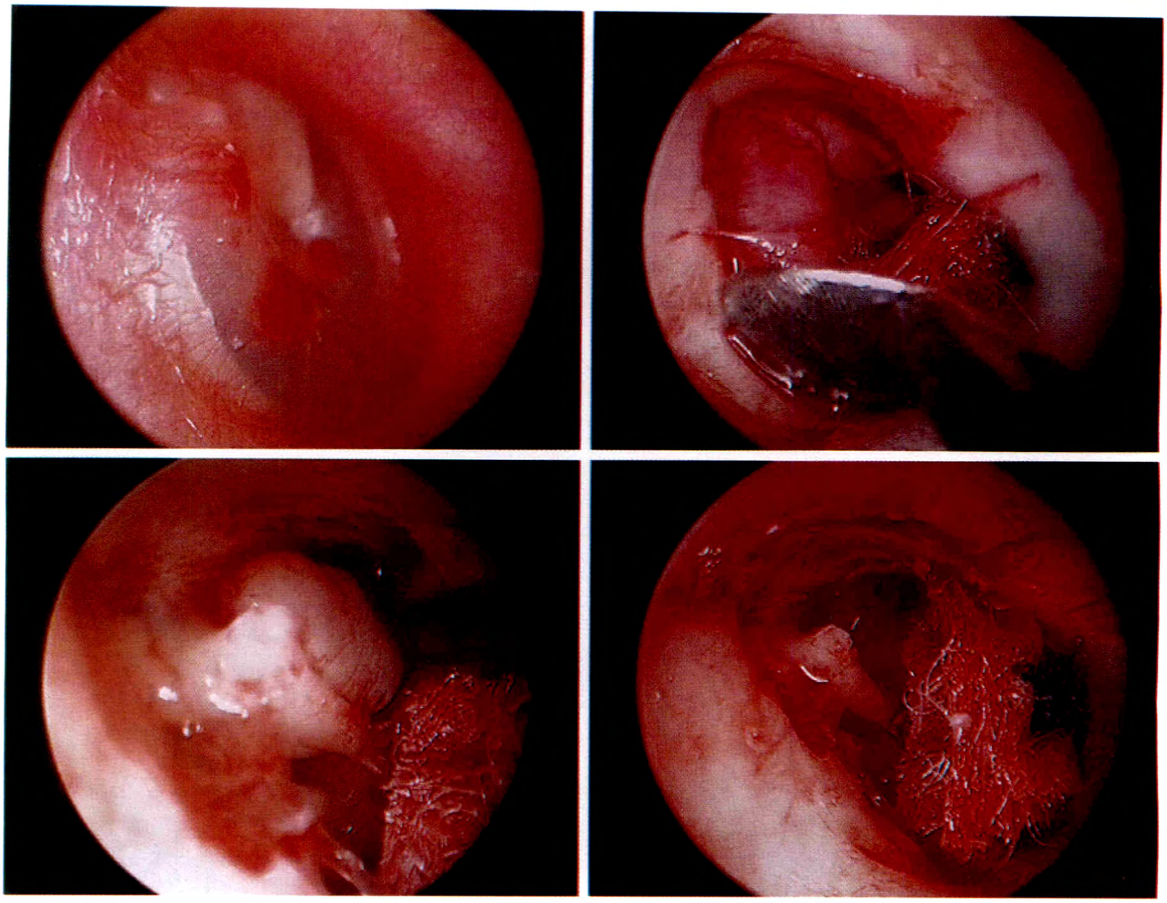


Fig 9. Right ear of 3-year-old child. Endoscopic removal of congenital cholesteatoma. Top left — endoscopic view of tympanic membrane. Top right — superiorly based tympanomeatal flap is being elevated. Bottom left — cholesteatoma is exposed anterior to malleus. Bottom right — middle ear inspection after removal of cholesteatoma.

and an object placed as far as possible from the distal tip of the scope while remaining in focus (far object distance). Given the need for magnification in ear surgery, it is not unusual for the endoscope to be used in very close relationship to the operative field (less than the near object distance), so that the image is out of focus. It is therefore essential to use a video camera to be able to adjust the focus of the camera to compensate for the loss of focus experienced at the level of the endoscope. It is exceedingly hard to perform otologic procedures directly off the endoscope.

There are 2 major safety concerns with endoscopic ear surgery. One is excessive heat dissipation. This was evident only when a xenon light source was used. Adequate illumination of the middle ear space can be accomplished with lower settings on the regular light source (because of the size of the cavity) without the need for xenon systems. As well, the tip of the endoscope requires continuous cleaning with antifog solution, which probably helps in cooling the endoscope.

The other safety concern is accidental patient movement with secondary direct trauma by the tip of the endoscope. The relatively large diameter of the endoscope I use (4 mm) and the anatomy of the ear canal and middle ear space will usually preclude the introduction of the endoscope beyond the tympanic ring. Even in endoscopic stapedectomy, there is little need for curetting the posterior and superior aspects of the canal for exposure; thus, there is a protective "rim" that prevents the advancement of the endoscope beyond the tympanic ring.

The many advantages of the endoscope include a wide angle of view. The endoscopic view usually includes the whole tympanic ring and ear canal at the same time. It is not defined by the narrowest segment of the ear canal. This provides a complete view of the middle ear space, tympanic membrane, and ear canal without the need for continuous repositioning of the surgeon's head and the microscope.

Another advantage is better visualization of structures that are parallel to the axis of the microscope. It is usually necessary to position structures at a right angle to the axis of the microscope for adequate visualization, which is difficult to impossible in cer-

SUMMARY OF PROCEDURES AND OUTCOME

Procedure	*No. of Ears*	*Main Outcome Measure*	*Success Rate*	*Complications*
Transcanal lateral graft tympanoplasty	32	Closure of perforation at 1-year follow-up; obtained in 22 patients	100%	Blunting of anterior sulcus in 3 patients and tympanic membrane cholesteatoma pearl formation in 1 patient
Transcanal medial graft tympanoplasty	64	Closure of perforation at 1-year follow-up; obtained in 48 patients	94%	None
Transcanal removal of congenital cholesteatoma	3	Lack of recurrence on clinical examination	No recurrence in 2 patients at 1 year	None
Stapedectomy	13	Closure of air-bone gap at 1-year follow-up	7 of 13 had 1-year follow-up; 6 of 7 had gap <10 dB (pure tone average of 0.5, 1, and 2 kHz); 1 patient had recurrence of conductive hearing loss	No sensorineural hearing loss (defined as >10 dB change in bone conduction at 0.5, 1, 2, and 3 kHz)
Transcanal removal of acquired cholesteatoma	53	Lack of recurrent disease on clinical examination at 1 year in 30 patients and at 2 years in 13 patients	29 of 30 patients were disease-free at 1 year, and 10 of 13 were disease-free at 2-year follow-up	No facial nerve injuries; 1 patient, who presented with perilymphatic fistula and sensorineural hearing loss, had 15-dB worsening of bone conduction at 3 kHz

tain situations. The 30° scope and the wide-angle 0° scope provide excellent visualization of structures such as the ear canal.

Another advantage is visualization of hidden structures such as an anterior tympanic membrane perforation and the sinus tympani, facial recess, attic, and hypotympanum. This is possible through a transcanal approach, even when using the 0° scope, because of the wide-angle view of the more recent endoscopes.

Another advantage is the ability to visualize past the shaft of larger surgical instruments such as drills. It is not uncommon in microscopic surgery for the handle of the instrument to prevent visualization of the operative field (after initial positioning and engagement) and for the surgeon to rely on the feel of the instrument rather than continuously visualizing the operative field.

Disadvantages of the endoscope include the loss of depth perception and binocular vision. This is easily compensated for with experience. In operative endoscopy, the introduction of the instrument into the field and the way it is visualized on the monitor provide for tactile and visual cues that are used by the experienced endoscopist to reconstruct a 3-dimensional view of the operative site. Even though newer endoscopes might provide that depth perception, this issue is more related to the experience of the surgeon than the limitation of the available scopes.

Another disadvantage is the one-handed surgical technique. This is probably the most important issue to deal with in endoscopic ear surgery. Meticulous attention to hemostasis is essential and this is easier given the excellent visualization of the ear canal and the ability to cauterize bleeding points along the edges of the incised skin in the canal — the most common site of bleeding in middle ear procedures. The tip of the endoscope could also be utilized to push or lift certain structures. Further development of endoscopic ear surgery might be enhanced by incorporating other functions into the endoscope.

Other disadvantages are the need for physician training and the cost of equipment. Acquiring the necessary skills should not be too difficult for the experienced nasal endoscopist. It might be rather hard for established otologists who lack endoscopic training to make the necessary transition. Most of the equipment used is available in most operating rooms. The only extra instruments are very minor modifications of the existing instruments. This cost is easily recuperated by less operative time and reduced inpatient days due to increased utilization of transcanal procedures.

The impact of the endoscope on middle ear surgery will have to be considered on the basis of the surgical task contemplated and the importance of these advantages and disadvantages in specific situations. The elevation of a tympanomeatal flap, for example, is done under direct vision with the endoscope, without the need for the continuous repositioning of microscopic surgery. It is difficult to tear a flap, since the angle of view includes both surfaces of the whole flap. It is relatively easy to identify and cauterize bleeding points along the incised edges of the skin of the ear canal.

In inspection of the middle ear space, the endoscope is the better instrument, for the above-discussed reasons. These include the ability for operative evaluation and treatment of disease within the facial recess, sinus tympani, hypotympanum, attic, and the anterior part of the tympanic cavity.

Positioning of a graft is much easier with the endoscope, given its wide angle of view that includes the tympanic ring along with the whole perforation and graft without the need for repositioning.

In positioning of a prosthesis, the unavailability of both hands (eg, to lift the malleus) and the lack of depth perception (assessing length of prosthesis needed) make this task more difficult with the endoscope.

Exploration and removal of a cholesteatoma is much easier with the endoscope, with less need for a postauricular approach for attic, limited mastoid, or facial recess disease.

Removal of diseased hypertrophied mucosa with the endoscope is difficult because of the need to suction out the continuous bleeding.

In drilling of the footplate, the ability to visualize past the shaft of the drill into the surgical field makes the endoscope a marginally superior instrument.

It is very difficult to use the endoscope and microscope to perform different tasks in the same procedure, and different surgeons will ultimately choose their instrument on the basis of their comfort level. Despite the relative safety of endoscopic stapedectomy and ossicular chain reconstruction, there are no compelling reasons for the adaptation of endoscopic techniques for these procedures.

The primary intention of this report is to give an overall view of this evolving technique. The number of cases, especially when broken down into different categories, is small, and it is quite hard to evaluate the endoscopic technique in comparison with traditional microscopic techniques for a wide variety of procedures and disorders in this early report.

CONCLUSIONS

There are many opportunities to utilize the endoscope in middle ear surgery, and outcome studies are needed to delineate advantages and disadvantages over the microscope. This preliminary study shows that the endoscope offers the greatest technical advantage in tympanoplasty and cholesteatoma surgery, and might increase utilization of transcanal over postauricular procedures.

REFERENCES

1. Thomassin JM, Korchia D, Doris JMD. Endoscopic guided otosurgery in the prevention of residual cholesteatomas. Laryngoscope 1993;103:939-43.

2. Sheehy JL, Anderson RG. Myringoplasty. A review of 472 cases. Ann Otol Rhinol Laryngol 1980;89:331-4.

3. Hawke M. Telescopic otoscopy and photography of the tympanic membrane. J Otolaryngol 1982;11:35-9.

4. Nomura Y. Effective photography in otolaryngology–head and neck surgery: endoscopic photography of the middle ear. Otolaryngol Head Neck Surg 1982;90:395-8.

5. Takahashi H, Honjo I, Fujita A. Transtympanic endoscopic findings in patients with otitis media with effusion. Arch Otolaryngol Head Neck Surg 1990;116:1186-9.

6. Poe DS, Bottrill ID. Comparison of endoscopic and surgical explorations for perilymphatic fistulas. Am J Otol 1994; 15:735-8.

7. McKennan KX. Endoscopic "second look" mastoidoscopy to rule out residual epitympanic/mastoid cholesteatoma. Laryngoscope 1993;103:810-4.

8. Rosenberg SI, Silverstein H, Willcox TO. Endoscopy in otology and neurotology. Am J Otol 1994;15:168-72.

9. Prescott R. Optical principles of endoscopy. J Med Primatol 1976;5:137-47.

Ann Otol Rhinol Laryngol 108:1999

APPLICATION OF LABELING TECHNIQUES TO ARCHIVAL TEMPORAL BONE SECTIONS

QING TIAN, MD
FRED H. LINTHICUM, JR, MD   ELIZABETH M. KEITHLEY, PHD
LOS ANGELES, CALIFORNIA

Pathology of the human inner ear has traditionally been studied in celloidin-embedded, hematoxylin and eosin–stained sections of the temporal bone. Although the traditional histologic approach has yielded valuable information, it is now possible to extend these studies to include analysis of molecules using immunohistochemical and histochemical staining techniques. Fourteen antibodies and 6 lectins have been applied to 420 archival, celloidin-embedded human temporal bone sections. Tissues had been fixed in 10% formalin, embedded in celloidin, sectioned, and stored for as many as 40 years. The staining intensities varied among sections, so they were ranked from "no label" to "dense label." To investigate the relationships between the extent of postmortem changes (PMCs), storage time, and staining intensity for each antibody, the sections were graded according to their PMCs, which ranged from good preservation of the temporal bone histologic structure to severe postmortem autolysis. Although statistical analysis indicated that both extent of PMCs and storage time in general decrease the staining intensity, both poorly fixed tissue and sections stored for a long time can yield good immunostaining results with some antibodies.

KEY WORDS — celloidin, cochlea, human, immunohistochemistry, inner ear, lectin.

INTRODUCTION

Otolaryngologists during the last century have been collecting temporal bone specimens from autopsies to prepare for histopathologic analysis of the ear. Because of the large size of the temporal bone and the desire to achieve the best microscopic section quality, celloidin was chosen as the embedding medium. It has strength, flexibility, and the ability to preserve very good cellular morphology in a tissue that has tough bone and delicate membranes suspended in fluid-filled spaces. These sections have yielded the pathologic information that is the cornerstone of otology.[1,2]

The cause of some otologic diseases has been particularly difficult to determine, and the potential unavailability of antigens in celloidin-embedded tissue has limited testing of hypotheses. Absence of animal models of certain diseases such as Meniere's disease and otosclerosis requires the research on pathogenesis to be based on human tissues. Even if good animal models are to be developed for human diseases, they need to be checked against human tissues at both the cellular and molecular levels.

In order to overcome these difficulties, during the last 10 years, researchers have collected fresh human temporal bone tissues and used more modern histologic techniques, including immunohistochemistry and in situ hybridization. However, frozen section studies of the human cochlea are limited by unavoidable damage to the tissues to be studied.[3]

The suitability of neutral buffered 10% formalin–fixed, decalcified, celloidin-embedded, archival temporal bone sections for immunohistochemical labeling of tissue antigens was first demonstrated by Wackym et al.[4] This was followed by efforts to improve the technique,[5-8] which included the application of "antigen retrieval" techniques. Celloidin sections between those that are used for hematoxylin and eosin (H & E) staining are stored in ethanol, making these sections available today for use with modern techniques such as immunohistochemical labeling of specific antigens that might be related to diseases of the temporal bone.

To make immunohistochemical labeling a useful technique, it is necessary to understand the variables that affect tissue labeling with antibodies or other reagents. This study was undertaken to systematically evaluate the current staining results relative to tissue storage time and the quality of the tissue fixation assessed by postmortem changes (PMCs).

MATERIAL AND METHODS

Temporal Bone Preparation. The temporal bones were collected 6 to 36 hours postmortem and fixed in neutral buffered 10% formalin for 4 weeks. The bones were decalcified in Versene (Spectrum Chemical Manufacture Co, Gardena, Calif) containing ethylenediaminetetraacetic acid (EDTA) until radiographs showed they were calcium free (4 to 6 months). They were then trimmed, dehydrated, and

---

From the House Ear Institute, Los Angeles, California. This work was supported by the Del E. Webb Foundation, Wickenburg, Arizona, the Kenneth T. and Eileen L. Norris Foundation, the House Ear Institute, and the Medical Research Service of the Department of Veterans Affairs.

CORRESPONDENCE — Fred H. Linthicum, Jr, MD, 2100 W Third St, Los Angeles, CA 91801.

embedded in celloidin; during these procedures, they were exposed to alcohol, ether alcohol, celloidin, and chloroform. Tissue sections were cut at 20 µm, and 1 in every 10 sections was stained with H & E and mounted. The unstained sections were kept in order and stored between numbered sheets of paper in 80% ethanol (pH 4 to 5). Some of these sections have been stored for as long as 40 years.

Antibodies and Lectins. Some of the sections evaluated for this report were also used for other studies.[9-12] The following antibodies were used: neurofilament for 68 kd and 200 kd polypeptides of neurofilament, B-lymphocyte antigen 36 (BLA 36) for B-lymphocytes, CD15 for neutrophils, CD43 for thymocytes, myeloid-specific antigen (BM3) for granulocytes and monocytes, T-cell (CD3) for activated T-cells, L26 for human B-cells (BioGenex, Inc, San Ramon, Calif), sodium- and potassium-activated adenosine triphosphatase (Na, K-ATPase) for Na, K-ATPase β2 (Upstate Biotechnology Inc, Lake Placid, NY), fibronectin (Accurate Chemical Co, Westbury, NY), leukocyte common antigen for lymphoid cells, CD45RB and 45CDRO for leukocytes, CD20 for B-cells, and CD3 for T-cells (Dako, Carpinteria, Calif). In cases in which 2 different antibody lot numbers were used, no obvious differences were observed.

Six lectins were purchased from Sigma Co (St Louis, Mo) to label carbohydrate moieties in the endolymphatic sac: wheat germ agglutinin (WGA) for β-D-N-acetylglucosamine, *Ricinus communis* agglutinin (RCA-120) for β-D-galactose, *Abrus precatorius* agglutinin (APA) for D-galactose, concanavalin A (Con A) for α-D-mannose and α-D-glucose, *Helix pomatia* agglutinin (HPA) for D-N-acetylgalactosamine, and *Ulex europaeus* agglutinin (UEA-1) for α-L-fucose.

Control Tissues. Paraffin- and celloidin-embedded animal and human tissues were used for positive controls and for development of the assays to conserve the temporal bone sections. They were not used in the analysis, however. These tissues were processed the same way as temporal bone tissues. Paraffin-embedded tissues included rat cochlea and human adenoid. Celloidin-embedded tissues included rat cochlea and human lung, kidney, adenoid, skin, spinal cord, and brain. Negative control tissue, known not to express the antigen of interest, was included in the assays to detect the possibility of spurious staining of temporal bone material.

Procedures Unique to Celloidin-Embedded Temporal Bone Sections. In general, the assays were performed as for any other tissue. There were a couple of steps, however, that had to be included or modified because of the celloidin and the large size of the sections. The first was removal of the celloidin, which could be done in several ways. A sodium hydroxide and methanol solution (saturated solution diluted 1:4 with methanol–antigen retrieval solution[5]) effectively dissolved the celloidin and presumably exposed tissue epitopes. Ten to 30 minutes were required for adequate removal of celloidin from sections. Acetone was used successfully for the Na, K-ATPase β2 subunit antibody labeling.[11] Following removal of celloidin, sections were hydrated and treated as any other tissue. Before antibodies were applied to the sections, 0.03% triton-X-100 was applied for 10 minutes to increase the permeability.

Handling of large sections with delicate, unsupported membranes requires special techniques to keep the sections intact during a histochemical assay. Sections can be mounted on slides coated with poly-L-lysine, gelatin, or aqueous mounting medium after the celloidin is removed and blotted until they are almost dry. The assay can also be run on free-floating sections, in 6-well tissue culture plates, that are mounted after the last step. A total of 420 celloidin-embedded human temporal bone sections labeled with different antibodies and lectins were used for the analysis in this study (Fig 1). Section handling was the most difficult component of the assay. It proved best to cut the sections with dissection scissors to make them smaller and remove unwanted, excess tissue. The celloidin sections were handled in either of 2 ways during the labeling procedure. The first was to adhere the sections to the glass slides. After cleaning, the slides were coated with poly-L-lysine solution and dried and stored. Before use, the slides were coated with aqueous mounting medium, and the sections were mounted, pressed flat, and heated on a slide warmer at 30°C. Just before the sections became dry, another layer of poly-L-lysine was applied on top of the section and pressed with filter paper and a roller. Then the sections were put into sodium hydroxide–methanol solution for 10 to 30 minutes and washed and processed. This is a good way to preserve the section and is convenient to use. One major problem is that the sections occasionally fall off the slides during subsequent steps. The free-floating method omitted the trouble of repeatedly putting the sections back on the slides, but required very careful handling of the sections.

Two chromogen systems were used to detect tissue antigen-antibody binding. The alkaline phosphatase and fast red detection system gave a bright red or dark pink color, which had better contrast with the yellowish brown color of the nonstained sections. Both color and black-and-white pictures had good contrast. Phosphatase-anti-phosphatase (PAP) and

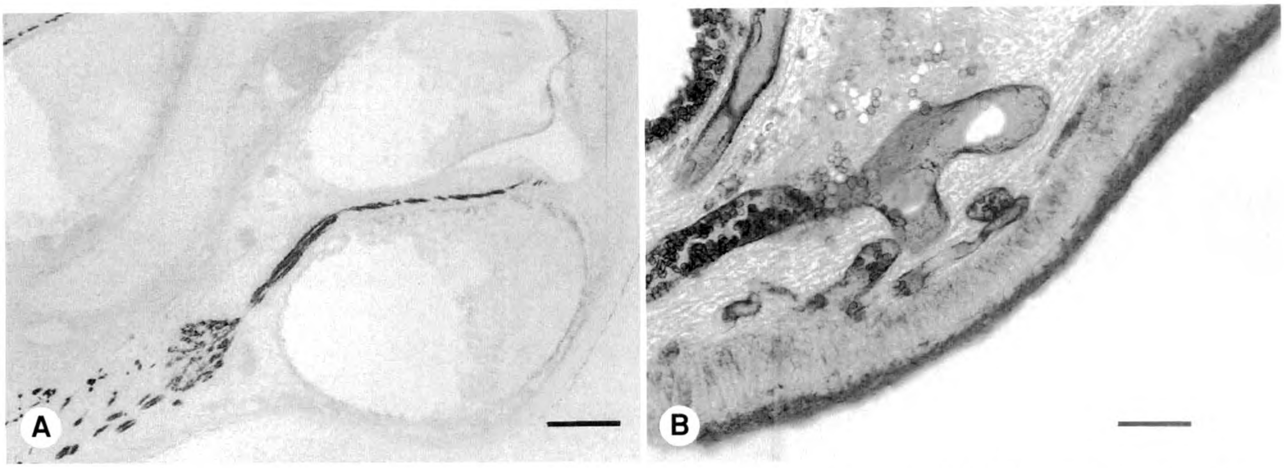


Fig 1. Light micrographs. Scale bars — 100 µm. Staining intensity score of "++++" was given to both of these sections. A) Archival, celloidin-embedded human temporal bone section immunolabeled with polyclonal antibody to neurofilament. Spiral ganglion cell bodies and their peripheral and central processes are labeled. B) Middle ear mucosa labeled with *Ulex europaeus* agglutinin (UEA) indicating presence of glycocalyx on surface of mucous membrane.

diaminobenzidine (DAB) staining also gave good results, but lacked strong contrast with the original color of the temporal bone sections. Adding 20 µm of 16% nickel chloride to the DAB solution before staining gave a dark brown or black color that provided excellent contrast for microscopy and photomicroscopy.

Most of the antibodies and lectin labeling did not require any enzyme digestion procedures to expose antigen or glycoconjugates. However, immunolabeling with antifibronectin antibody was improved with preincubation with ficin. The ficin solution was diluted 1:2 or 1:4 and applied to the sections for 10 to 30 minutes (60°C) before the immunolabeling procedure. Blocking for nonspecific background labeling of tissues was achieved by incubation of the sections in 0.5% casein or dry milk, 0.5% bovine serum albumin, serum from the animal in which secondary antibody was made, or combinations of the above.

Tissue Analysis. The staining results of 420 sections were graded as follows: – (negative); + (weak positive); ++ (obvious staining); +++ (strong staining); and ++++ (strongest staining). When more than 1 section from 1 temporal bone was stained with the same antibody, the average staining result was recorded.

For analysis, the bones were placed into 1 of 4 groups based on storage time: 1 to 10 years, 11 to 20 years, 21 to 30 years, or 31 to 40 years. Storage years were calculated from the year the bone was collected to the year the staining was conducted.

Postmortem changes were graded for each temporal bone by using the originally mounted H & E sections adjacent to the immunohistochemically stained section as follows: PMC-1, intact inner and outer hair cells, stereocilia visible on the cuticular plate without stria or saccular fragmentation; PMC-2, hair cells identifiable but distorted with stereocilia visible, and no stria or saccular fragmentation; PMC-3, fragmentation of the organ of Corti, with discernible hair cells, stria vascularis, saccule, and macula; and PMC-4, total disruption of the organ of Corti and fragmentation of the stria vascularis, saccule, and macula.

RESULTS

The intensity of label was evaluated according to the scale described in Material and Methods and illustrated in Fig 1. When more than 1 section from an individual temporal bone was stained with the same antibody, there was little variability among sections. The labeling intensity scores for all labels combined were plotted against the section storage time, as shown in Fig 2. The most significant factor affecting the immunohistochemical staining of celloidin-embedded human temporal bone sections was the section storage time (Kendall $\tau = -.25$, $p < .001$). There were 71 sections that had been stored for 1 to 10 years, 210 sections for 11 to 20 years, 134 sections for 21 to 30 years, and 5 sections for 31 to 40 years. The largest percent of well-stained tissue sections came from temporal bones that had been stored for 10 years or less. The largest number of poorly stained sections came from bones that had been stored for 31 to 40 years. However, very good staining was achieved in individual sections stored up to 30 years, and satisfactory staining may be achieved in sections stored up to 40 years.

The distribution of stain intensity relative to the PMC score for all the antibodies and lectins combined is shown in Fig 3. A score of PMC-1 indicates

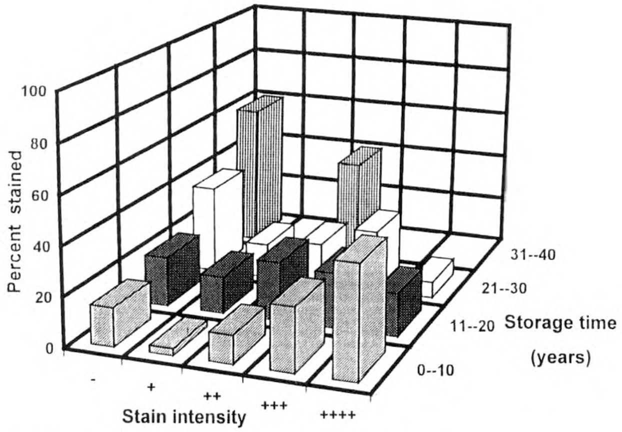


Fig 2. Staining intensity of different storage time groups was compared. Results show that when all sections labeled with all different antibodies tested are combined, there is statistically significant correlation between storage time and staining (p < .01), indicating that long storage time may yield weaker staining.

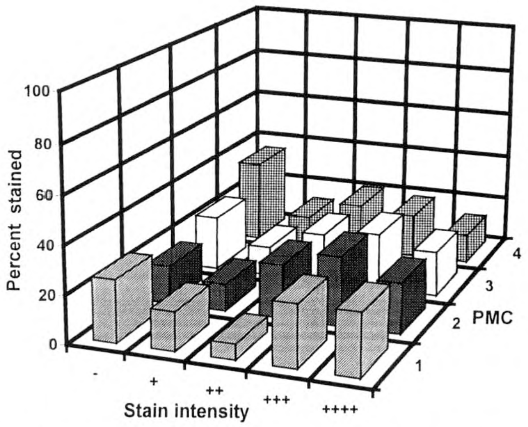


Fig 3. Staining intensity as function of tissue preservation is shown for all sections combined, independent of antibody or lectin used in assay. Small, though statistically significant, relationship was seen with postmortem change (PMC; see text for system of scoring) groups. PMC is not major factor affecting staining intensity.

good tissue preservation, and PMC-4 represents poor preservation. There were 30 sections in the PMC-1 category, 62 sections in the PMC-2 category, 232 sections in the PMC-3 category, and 96 sections in the PMC-4 category. Although the relationship between PMC score and stain intensity was statistically significant (Kendall $\tau = -.11$, $p > .002$), the correlation coefficient was quite small, and PMC score need not have much impact on the practical choice of sections. Sections with the poorest tissue preservation were more likely to yield unusable data, but it is also possible to achieve good staining of these sections.

In order to determine whether the relationship of staining intensity to storage time or PMCs was particular to any 1 antibody or lectin, 4 individual antibodies (Fig 4) and 5 lectins (Fig 5), each with more than 20 sections stained, were analyzed individually. These results are plotted to show the relationships among the staining intensity, the storage years, and PMCs. Antifibronectin, antineurofilament, and Dako LCA showed a tendency of decreased staining intensity with increasing storage time. Anti–Na, K-ATPase, APA, WGA, HPA, and UEA showed staining intensity not closely related to the number of storage years or to PMCs. In most cases, Con A had weak staining.

DISCUSSION

Understanding of diseases and normal cellular organization of the temporal bone and inner ear has evolved because of many years of analysis of the relationships among inner ear pathology as seen in H & E–stained sections, disease, and hearing loss.[1,13] The advent of immunohistochemical and lectin histochemical techniques has now made possible the in situ localization of antigens and molecules on the cellular level and greatly advanced the understanding of basic biological mechanisms and also the biology of disease in the inner ear.[3,14-16] The possibility of using immunohistochemical techniques on stored celloidin-embedded tissue sections from the temporal bone banks is therefore of great significance.[4] Immunohistochemical techniques were improved by the addition of a sodium hydroxide–methanol treatment to remove the celloidin and resulted in stronger immunohistochemical labeling of keratin, vimentin, neurofilament, and S-100.[5] It is hypothesized that the treatment with strong alkaline solution reverses the protein cross-link caused by formalin fixation of the tissue.[5] Other solvents for removing celloidin that also seem to allow for good immunohistochemical staining are acetone,[11] clove oil,[4] and methanol. Comparisons among these 3 solvents using anti–Na, K-ATPase showed denser label and less background with the acetone.[11] It seems, therefore, that for the best labeling results, several methods should be tried with each antibody. Antigen retrieval with citrate buffer and microwaves, successfully used for other tissue,[5,17,18] was tried with some antibodies in this study without good results. The different tissues in the celloidin sections shrank differentially at temperatures over 60°C, so that the sections were difficult to interpret. It seems that enzymatic digestion may be the best method for increasing epitope availability.

Either EDTA or trichloroacetic acid is generally used for decalcification of temporal bones. Presumably, the method of tissue decalcification is important for the quality of immunostaining, and although EDTA (Versene) works slowly to decalcify bone (>4 months), it preserves tissue antigenicity. Destruction

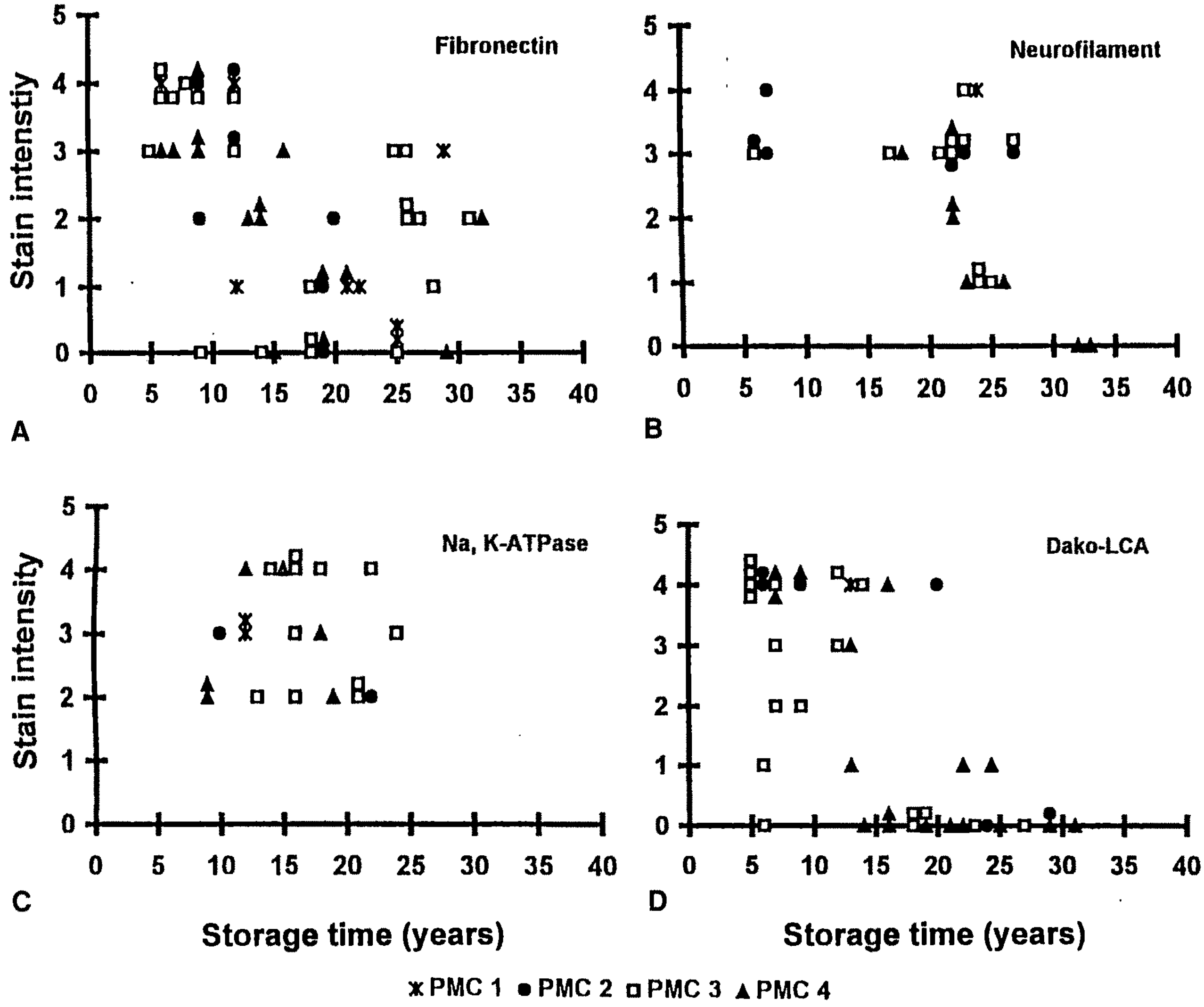


Fig 4. Relationship of staining intensity and PMC to antibodies. A) Fibronectin stain of 49 cases. Staining intensity decreases as storage time increases. This occurs in both well-preserved and poorly preserved sections. For this antibody, storage time affects staining intensity more than quality of sections. B) Neurofilament stain of 26 cases. Storage time does not affect stain intensity. PMC may have some influence on stain intensity, because all sections stained at intensity below grade 2 have PMC 3 or 4, which means bad preservation. C) Sodium- and potassium-activated adenosine triphosphatase (Na, K-ATPase) stain of 21 cases. Storage time and PMC do not affect staining intensity of sections. D) Dako leukocyte common antigen (LCA) stain of 42 cases. Shorter storage time relates to stronger stain intensity, while weaker stain appears more likely in sections stored for more than 10 years. PMC does not seem to be obvious factor affecting stain intensity.

of both cytomegalovirus viral antigens and DNA was reported by Michaels et al[19] in tissue known to be infected with cytomegalovirus when decalcified in formic acid.

The sections used in the current study were stored in 80% ethyl alcohol for 0.5 to 40 years. It is necessary when planning a study to know how this factor affects the immunohistochemical staining pattern, because it can affect the choice of sections. Shorter storage times yielded better staining results for some of the antibodies and lectins, but not necessarily others. This may be caused by tighter binding of the celloidin to the tissue or loss of antigenicity due to degradation of the epitope with the progression of time. Some antigens seemed to be unaffected by the storage time. Prolonged storage in fixative prior to embedding of tissue has also been shown to degrade the quality of immunolabel,[20,21] so it is probably better to embed and section the temporal bones than to store them in fixative for long periods of time.

It is generally accepted that rapid application of fixative to tissue results in fewer PMCs and, therefore, superior structural preservation. This also seems true for immunohistochemical labeling of tissue antigens, which are subject to breakdown by proteolytic enzymes. For this reason, the ability to immunolabel antigens in human tissue that remained unfixed for many hours could be compromised. Tissue preser-

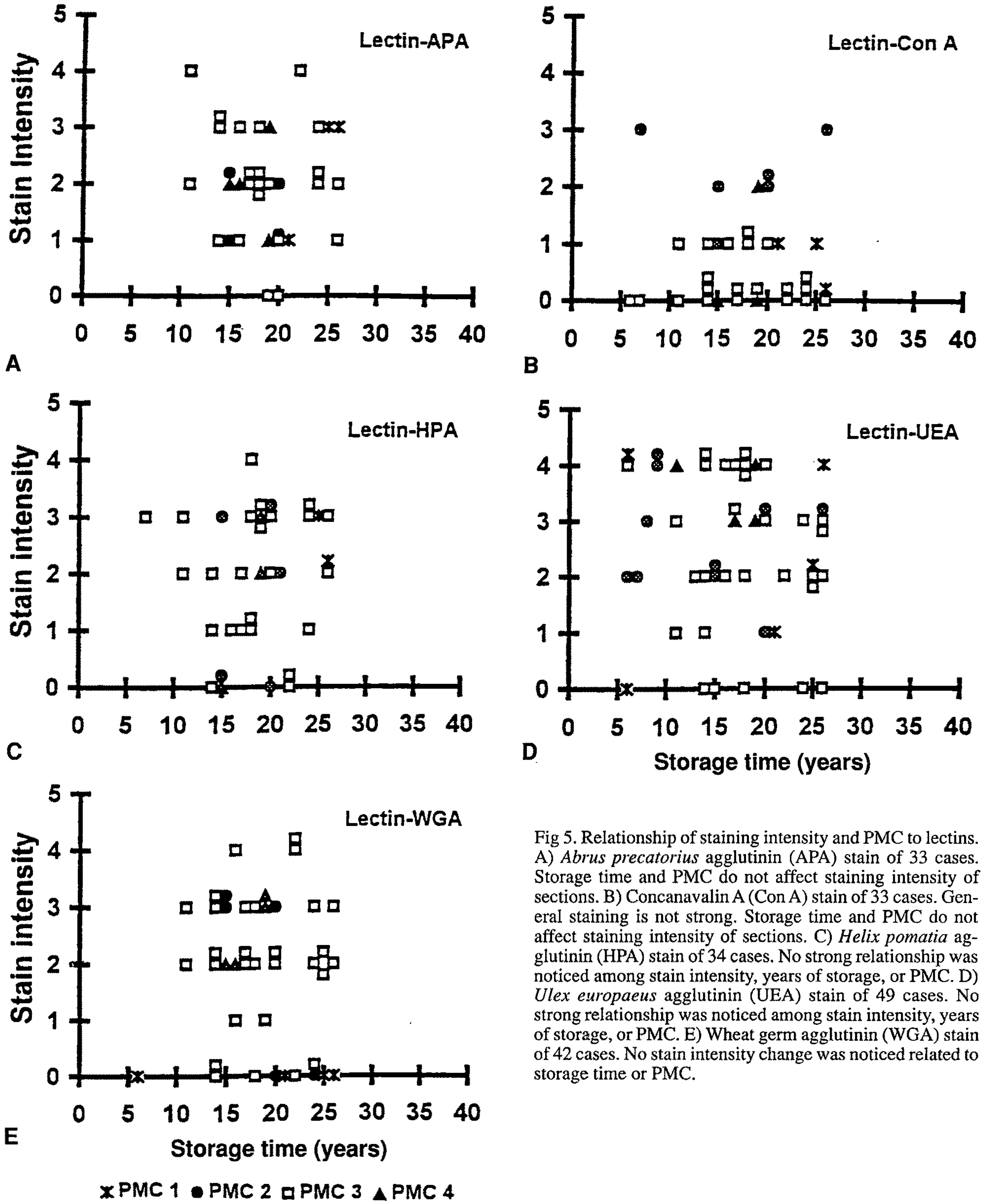


Fig 5. Relationship of staining intensity and PMC to lectins. A) *Abrus precatorius* agglutinin (APA) stain of 33 cases. Storage time and PMC do not affect staining intensity of sections. B) Concanavalin A (Con A) stain of 33 cases. General staining is not strong. Storage time and PMC do not affect staining intensity of sections. C) *Helix pomatia* agglutinin (HPA) stain of 34 cases. No strong relationship was noticed among stain intensity, years of storage, or PMC. D) *Ulex europaeus* agglutinin (UEA) stain of 49 cases. No strong relationship was noticed among stain intensity, years of storage, or PMC. E) Wheat germ agglutinin (WGA) stain of 42 cases. No stain intensity change was noticed related to storage time or PMC.

vation, therefore, was assessed as a potential variable in the quality of immunolabeling of the archival sections. All the temporal bones at the House Ear Institute temporal bone bank were fixed in 10% formalin 6 to 36 hours postmortem and were stored in that fixative until they were processed. Analysis of the PMCs was made by judging the H & E–stained sections for the condition of the inner ear tissue. As shown in Fig 3, in general, there was not a good relationship between the PMC score and the quality of the immunolabel. Although this is an unexpected finding, it has good practical implications and certainly increases the number of tissue sections available for immunoassays. Although the greatest number of poorly stained sections had a PMC score of 4, excellent labeling could be achieved in such sections. It seems, therefore, that these temporal bones should still be included in an immunohistochemical study and that several sections from the bone should be evaluated. It is possible that the PMC measure of tissue preservation is not accurate enough to determine which bones have degraded antigens, but at this time, there are no better measures available.

Because many clinical issues that may be addressed in the archival tissue involve identification of abnormality, it is necessary to assay simultaneously some known tissue containing the antigen to be assured that the results obtained with the immunohistochemical technique are correct. In the present study, this control over the results was achieved by developing each immunoassay on tissue, either rat or human, in which the antigen expression pattern is well known. This tissue was treated similarly to the human temporal bone with respect to the fixative, decalcification, and embedding in celloidin. When the human temporal bones were assayed, this control tissue was also assayed, and the labeling pattern was confirmed before interpretation of the human temporal bone sections was made.

In conclusion, it is recommended that each antibody to be used on stored, celloidin-embedded temporal bone sections be tested empirically with the various standard immunohistochemical tools to yield the best tissue labeling (Figs 4 and 5). These include the time in sodium hydroxide–methanol solution, the protease digestion of antigens, and tissue blockers. It seems that all sections in the collection are theoretically useful for immunoassays. Both poorly fixed tissue and sections stored for a long time can yield good immunolabeling with some antibodies.

REFERENCES

1. Schuknecht HF. Pathology of the ear. 2nd ed. Philadelphia, Pa: Lea & Febiger, 1993:16-9.
2. Linthicum FH Jr, Schwartzman JA. An atlas of micropathology of the temporal bone. San Diego, Calif: Singular Publishing Group, 1994.
3. Arnold W. Immunohistochemical investigation of the human inner ear. Acta Otolaryngol (Stockh) 1988;105:392-7.
4. Wackym PA, Micevych PE, Ward PH. Immunoelectron microscopy of the human inner ear. Laryngoscope 1990;100: 447-54.
5. Shi SR, Cote C, Kalra KL, Taylor CR, Tandon AK. A technique for retrieving antigens in formalin-fixed, routinely acid-decalcified, celloidin-embedded human temporal bone sections for immunohistochemistry. J Histochem Cytochem 1992;40:787-92.
6. Shi SR, Tandon AK, Haussmann RR, Kalra KL, Taylor CR. Immunohistochemical study of intermediate filament proteins on routinely processed, celloidin-embedded human temporal bone sections by using a new technique for antigen retrieval. Acta Otolaryngol (Stockh) 1993;113:48-54.
7. Shi SR, Chaiwun B, Young L, Imam A, Cote RJ, Taylor CR. Antigen retrieval using pH 3.5 glycine-HCl buffer or urea solution for immunohistochemical localization of Ki-67. Biotech Histochem 1994;69:213-5.
8. Shi SR, Imam SA, Young L, Cote RJ, Taylor CR. Antigen retrieval immunohistochemistry under the influence of pH using monoclonal antibodies. J Histochem Cytochem 1995;43: 193-201.
9. Tian Q, Rask-Andersen H, Linthicum FH Jr. Identification of substances in the endolymphatic sac. Acta Otolaryngol (Stockh) 1994;114:632-6.
10. Keithley EM, Tian Q. Fibronectin-like immunoreactivity of the basilar membrane of celloidin-embedded human temporal bone sections. Acta Otolaryngol (Stockh) 1994;114:613-9.
11. Keithley EM, Horowitz S, Ruckenstein MJ. Na,K-ATPase in the cochlear lateral wall of human temporal bones with endolymphatic hydrops. Ann Otol Rhinol Laryngol 1995;104: 858-63.
12. Linthicum FH Jr, Tian Q, Slattery W III. Marrow-mesenchyme connections in the fetal and newborn tympanum. A new entity. Ann Otol Rhinol Laryngol 1997;106:466-70.
13. Merchant SN, Schuknecht HF, Rauch SD, et al. The National Temporal Bone, Hearing, and Balance Pathology Resource Registry. Arch Otolaryngol Head Neck Surg 1993;119: 846-53.
14. Lim DJ, Coticchia JM, Ueno K, Heiselman FA, Bakaletz LO. Glycoconjugates in the chinchilla tubotympanum. Ann Otol Rhinol Laryngol 1991;100:933-43.
15. Anniko M, Arnold W. Methods for cellular and subcellular visualization of intermediate filament proteins in the human inner ear. Acta Otolaryngol Suppl (Stockh) 1990(suppl 470):13-22.
16. Schrott-Fisher A, Egg G, Kong W-J, Renard N, Eybalin N. Immunocytochemical detection of choline acetyltransferase in the human organ of Corti. Hear Res 1994;78:149-57.
17. Gown AM, de Wever N, Battifora H. Microwave-based antigenic unmasking. A revolutionary new technique for routine immunohistochemistry. Appl Immunohistochem 1993;1: 256-66.
18. Szekeres G, Audouin J, Le Tourneau A. Is immunolocalization of antigens in paraffin sections dependent on method of antigen retrieval? Appl Immunohistochem 1994;2:137-40.
19. Michaels L, Soucek S, Liang J. The ear in the acquired immunodeficiency syndrome: I. Temporal bone histopathologic study. Am J Otol 1994;15:515-22.
20. Sillevis-Smitt PAE, van der Loos C, Vianney de Jong JMB, Troost D. Tissue fixation methods alter the immunohistochemical demonstrability of neurofilament proteins, synaptophysin, and glial fibrillary acidic protein in human cerebellum. Acta Histochem 1993;95:13-21.
21. Taylor CR, Shi SR, Chaiwun B, Young L, Imam SA, Cote RJ. Strategies for improving the immunohistochemical staining of various intranuclear prognostic markers in formalin-paraffin sections: androgen receptor, estrogen receptor, progesterone receptor, p53 protein, proliferating cell nuclear antigen, and Ki-67 antigen revealed by antigen retrieval techniques. Hum Pathol 1994;25:263-70.

Ann Otol Rhinol Laryngol 108:1999

OPTICAL TRACKING OF A MICROSCOPE FOR IMAGE-GUIDED INTRANASAL SINUS SURGERY

ROLF HAUSER, MD BIRGIT WESTERMANN, MSC, PHD
BASEL, SWITZERLAND

The objective of this study was to examine the effects of optical and tracking properties on the accuracy of an optically locatable operating microscope. The intraoperative arrangement was based on experimental results obtained from a skull model. Measurements were taken from 24 patients undergoing intranasal microscopic sinus surgery for various disorders. Two major groups of influencing factors were determined from measurements on the model: 1) optical properties of the microscope, such as the method of focal point adjustment, focal length, and magnification of the lens; and 2) tracking properties of the microscope, such as the distance of the digitizer to the tracked object, the number of reference infrared light–emitting diodes (IR-LEDs), and the area circumscribed by these IR-LEDs. Patient measurements showed an overall spatial error of 2.39 ± 1.15 mm with a laser-supported adjustment of the focal point of the microscope. Although the associated 95th percentile was at 4.36 mm, such a value is encouraging for further development of microscopically navigable systems. It must be noted that the noninvasive patient-to-image registration was performed on the basis of a computed tomographic image with a slice distance of 2 mm.

KEY WORDS — image-guided surgery, intranasal surgery, locatable operating microscope, optical digitizing.

INTRODUCTION

Identifying the intraoperative disorder precisely and locating critical neighboring anatomic structures exactly is of paramount importance in paranasal sinus surgery. As modern medical imaging technology is capable of displaying high-resolution, multidimensional data sets dynamically, there is little doubt that these visualization methods may enhance the surgeon's spatial orientation. For intraoperative application, such methods have to correlate accurately the patient's positional information with preoperatively acquired image data to support 3-dimensional (3-D) treatment planning and guidance. In order to improve the surgeon's spatial orientation, a fast and reliable 3-D patient registration method[1,2] was developed that allows registration of the patient-to-image data and optical tracking of both the position and orientation of the patient's head and of the operating microscope.

As described by several investigators,[2-6] an operating microscope can be used not only for visualization of anatomic structures, but also as a navigational device for a 3-D guided approach to the patient's disease. However, targeting with a locatable microscope is different from targeting with a surgical instrument. The instrument's trajectory is defined by its origin and tip as the rigid end of the longitudinal axis, which can be used to locate anatomic structures or to plan a surgical approach to hidden structures by touching the operative site. In contrast to the geometrically predefined tip of the instrument, the microscope's focal point and associated optical trajectory have to be localized. Both parameters are indispensable prerequisites for a reliable determination of the microscope's spatial position and orientation in relation to the patient's disorder.

The purpose of this study was to analyze the effects of optical and tracking properties on the accuracy of an optically locatable microscope by identifying factors that contribute significantly to its targeting accuracy. On the basis of experimental results, parameters were optimized and measurements performed in patients during intranasal surgery.

MATERIALS AND METHOD

Optical Digitizing System. The localization system is based on a 3-D optical digitizing unit (PixSys Inc, Boulder, Colo). It consists of a camera boom assembly with 3 linear high-resolution cameras and a computer. The digitizer is mounted on a mobile stand. The system is interfaced to a workstation providing the transfer of spatial coordinates of infrared light–emitting diodes (IR-LEDs). A schematic view of the system is shown in Fig 1.

Optically Navigable Operating Microscope. A reference frame with 13 embedded IR-LEDs was attached to the casing of the microscope (M 695, Leica AG, Heerbrugg, Switzerland). The intention to use a spatially distributed arrangement of IR-LEDs around the base unit of the microscope was to bring them into a relatively close relation to the focus.

From the Department of Otorhinolaryngology, University of Basel, Kantonsspital, Basel, Switzerland. This work was supported by the Kommission für Technologie und Innovation, Project-Nr. 3106.1 (Hauser), Bern, Switzerland.

CORRESPONDENCE — Rolf Hauser, MD, Dept of Otorhinolaryngology, University of Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

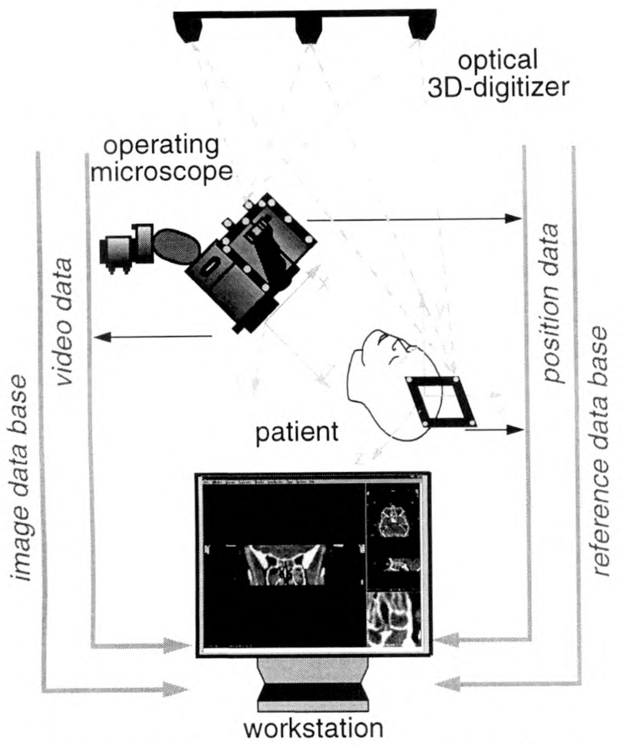


Fig 1. Schematic of image-guided system for application in intranasal microscopic sinus surgery. Patient and microscope are tracked throughout surgery with infrared light–emitting diodes (IR-LEDs).

Since the microscope's position and orientation are defined by the trajectory between the focal point and its origin in the principal plane of the lens, the localization of the IR-LEDs close to the rotational axes would minimize the a priori error of the focal point.

During intraoperative targeting, the focal point has to be readjusted by determining the focal plane, that is, the plane of greatest visual resolution. This can be achieved either by simple visual adjustment or with a laser-supported method.

Because simple visual adjustment of the focal plane to obtain a clear and sharply defined image of the microscope's field of view is very critical due to the high depth of focus and to individual refraction anomalies, it may influence the accuracy of tracking. Therefore, in order to minimize the focusing error, a recently developed laser module (Leica AG) was inserted between the ocular unit and the optical base unit of the microscope. The method for a laser-supported adjustment uses 2 red crossing laser beams (wavelength 635 nm) that indicate the difference between the real position of the focal point and the calibrated position. The exact focusing can be controlled by the overlay position of both lasers in the microscope's field of view. Superimposing the 2 light marks shows that the focal plane has been reached by maximal focusing and therefore the focal point is exactly adjusted to its calibrated position. After adjusting the focal point, its position and orientation are calculated from the 3-D data obtained from signals generated by the pulsed IR-LEDs fixed at the microscope. At least 3 noncolinear IR-LEDs must be detected by the optical digitizer to determine the microscope's optical trajectory relative to the digitizer coordinate system. Finally, the focal point coordinates are transformed into the reconstructed patient coordinate system by means of the IR-LEDs on the patient's reference panel and correlated to the preoperative computed tomography (CT) images.

Registration and Referencing System. A patient registration and referencing system, described earlier in detail by Westermann and Hauser[1] and Hauser et al,[2] was applied. It is structured upon a dental face-bow. Attachment to the external auditory canals, the nasion, and the upper teeth guarantees a tight and reliable fixation of the face-bow to the patient's head. A Plexiglas box with N-shaped, x-ray–absorbing fiducial markers was added to the face-bow during CT. The system was readapted to the plastic skull model or, intraoperatively, to the patient. An additional quadratic panel with 4 IR-LEDs was fixed to the face-bow. Thus, the position of the head was tracked continuously, and the head could be moved without a time-consuming recalibration procedure to establish the patient-to-image transformation.

Data Preprocessing. An automatic algorithm detects the position of the fiducial markers (9 markers per image). A transformation matrix that maps 2-dimensional image coordinates to 3-D reference coordinates can be calculated to correct the image plane and center. The matrix takes into account misalignment and motion of the patient's head as rigid body translational and rotational motions. Therefore, errors caused by the patient's movements or an incorrect alignment of the head during CT data acquisition may be eliminated.

Data Presentation. The CT image data (2-mm slice thickness and 2-mm table incrementation; Siemens Somatom DRH, 125 kV, 5-second measuring time) are displayed on a computer screen. The image space location of the focus of the microscope is recorded and compared to the location of the corresponding marker and anatomic landmarks. The actual position and orientation of the microscope's focus are represented by crosshairs in 3 orthogonal views (axial, coronal, sagittal) on a computer screen during measurements.

Measurements. Measurements determining the microscope's spatial error were performed on a plastic skull model and on 24 patients undergoing intrana-

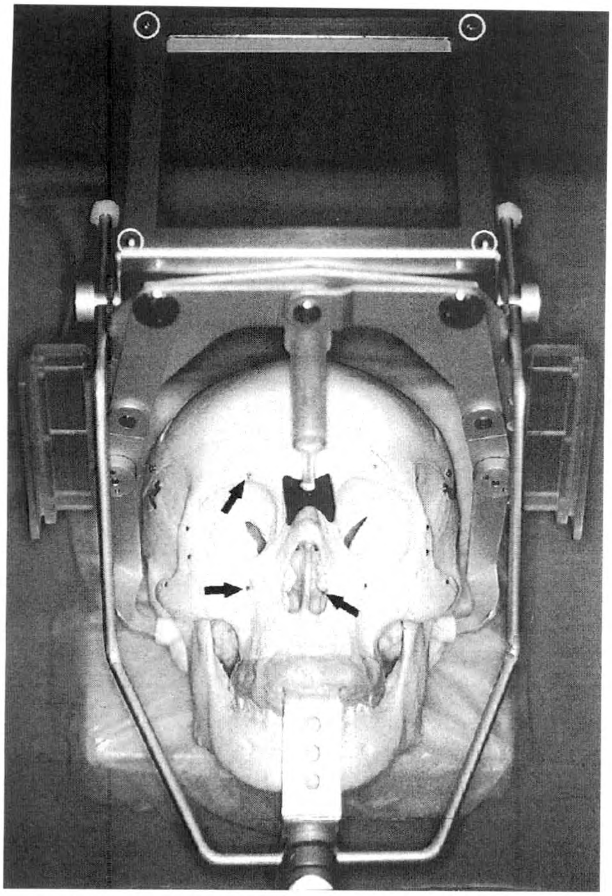


Fig 2. Plastic skull model used for accuracy studies, with face-bow attached. Three of 18 x-ray–absorbing marker spheres are indicated by arrows, and 4 IR-LEDs of reference frame panel are surrounded by circles.

sal sinus surgery for different disorders. To determine the absolute deviation of the microscope's focal point position from the position of a reference point, eg, an artificial marker or anatomic landmark, the euclidean distance was computed. This deviation will be referred to as the spatial error of the microscope. For statistical evaluation, the software program SigmaPlot 3.0 (Jandel Scientific GmbH, Germany) was used.

For the plastic skull model, 18 x-ray–absorbing, 2-mm marker spheres were fixed to the plastic skull and were distributed on the face along the intranasal surface. The CT data were acquired with the face-bow attached. Figure 2 shows the model positioned on an operating table with the face-bow and the reference panel attached. The marker spheres were numbered consecutively and identified on the CT images by a mouse-driven cursor to determine their 3-D location. During testing, the markers were selected in a random order and each position was measured 30 times. The following tests were conducted.

For the simple visual and laser-supported adjustment, the digitizer was positioned at a distance of 1.5 m from the object. The angle between the digitizer's longitudinal axis and the plane of the head reference panel was 45°. These conditions were kept constant during the ongoing measurements. The positions of 3 marker spheres (insertion of the lower nasal concha; roof of the ethmoid; anterior wall of the sphenoid) were measured with increasing magnification of 2.8× to 14.4× for simple visual and laser-supported adjustment of the focal point. The focal length of the lens was 250 mm. With the maximum magnification of the microscope, the influence of focal length on accuracy was measured for lenses of 250, 300, and 350 mm.

For the laser-supported adjustment, measurements were performed with the maximum magnification of 14.4× and a lens with a focal length of 250 mm. The effect of systematic variation of the distance between the digitizer and the model (middle point of the reference panel) was tested. It varied from 1.5 to 3.0 m in 0.5-m steps. The angle between the digitizer and the plane of the reference panel was adapted such that the microscope was located in the field of view of the digitizer. The influence of the number of detected IR-LEDs attached to the microscope, and their geometric relationship as the calculated area comprising those IR-LEDs, was examined. The measurements were performed such that a minimum of 3 and a maximum of 12 IR-LEDs were detected. The distance of the digitizer was 1.5 m, with the angle fixed at 45° to the reference panel.

Patients. Twenty-four patients with diseases of the paranasal sinuses (n = 23) and the orbita (n = 1) were treated. A CT scan of the patient's head with the face-bow attached for registration was taken 1 day before surgery. On the basis of the experimental results, the intraoperative arrangement of the system was chosen. For the measurements, the distance and angle of the optical digitizer were kept constant at 1.5 m and 45°, respectively, and the focal length of the microscope was set at 250 mm at a magnification of 14.4×. At least 4 IR-LEDs of the microscope and all 4 IR-LEDs of the patient reference panel had to be detected by the digitizer for a single measurement. It could then be assumed that the measurement was reliable for clinical decision making. For the determination of accuracy of the method, 5 points were selected and the measurements were made with the microscope focus adjusted simply visually (n = 10 patients) and by using the laser module (n = 14). Two of the reference points were part of the face-bow (nasal pillar and earplug), and 3 were anatomic landmarks (the medial canthus, the anterior end of the insertion of the middle concha, and the anterior end of the insertion of the inferior nasal concha). All

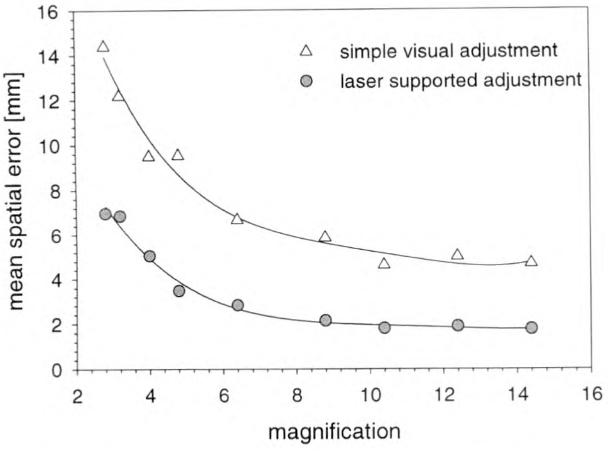


Fig 3. Dependency of spatial error on magnification of lens with focal length of 250 mm. Thirty measurements were performed for single marker at each magnification step.

TABLE 1. SUMMARY OF STATISTICAL VALUES FOR VISUAL AND LASER-SUPPORTED ADJUSTMENT OF FOCAL POINT AT DIFFERENT FOCAL LENGTHS IN PLASTIC SKULL MODEL

	Simple Visual Adjustment Error (mm)			*Laser-Supported Adjustment Error (mm)*		
	f = 250 mm	*f = 300 mm*	*f = 350 mm*	*f = 250 mm*	*f = 300 mm*	*f = 350 mm*
Mean	1.46	1.95	2.54	1.18	1.49	1.79
SD	0.68	0.68	0.71	0.39	0.51	0.64
SE	0.03	0.02	0.03	0.02	0.02	0.03
95th Percentile	2.82	3.31	3.96	1.95	2.51	3.07
Maximal value	3.89	4.14	4.30	2.49	3.26	3.51

f — focal length of lens.

of these points were identified and marked on the CT images. Each position was redetermined 20 times intraoperatively with the microscope.

RESULTS

Plastic Skull Model. Throughout measurements, the mean spatial error was smaller for the laser-supported adjustment of the focus than for the simple visual adjustment. The mean values of the magnification-dependent error are presented in Fig 3. They were fitted by a regression of the fourth order. The mean spatial error and the associated standard deviation ranged from 14.39 ± 0.19 mm for the minimum to 4.67 ± 0.17 mm for the maximum magnification and the simple visual adjustment, and from 6.96 ± 0.23 to 1.76 ± 0.18 mm for the laser-supported adjustment. Therefore, the magnification contributes substantially to the overall error. Figure 4 illustrates the comparison of both methods for different focal lengths at the maximum magnification. For the simple visual adjustment, the mean spatial error varied from 1.46 ± 0.68 mm for the 250-mm focal length to 2.54 ± 0.71 mm for a focal length of 350 mm. The 95th percentile of the error was between 2.82 and 3.96 mm, accordingly. With the laser module, the accuracy was consistently better, with the mean spatial error ranging from 1.18 ± 0.39 to 1.79 ± 0.64 mm and a 95th percentile between 1.95 and 3.07 mm. Therefore, with increasing focal length, the mean spatial error increased. Table 1 summarizes the results for the different focal lengths.

Figure 5 illustrates the behavior of the overall error for an increasing distance of the optical digitizer from the measured object. The data were approximated by a polynomial function of the second order. The mean spatial error was 1.18 ± 0.39 for the 1.5-m distance and 9.75 ± 2.3 for 3.0 m, with the associated

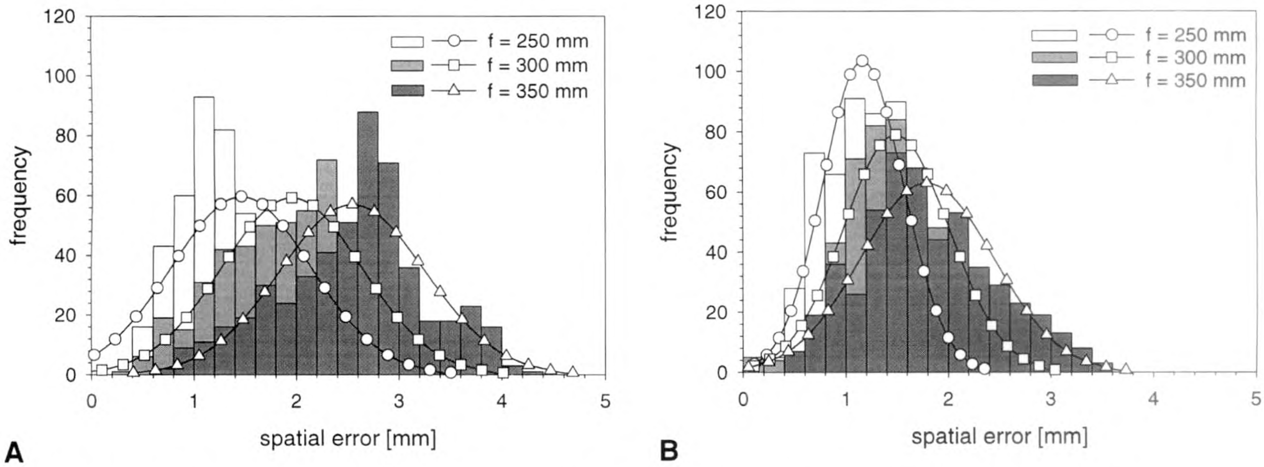


Fig 4. Distribution of spatial error for measurements with different focal lengths (f). Error histograms were fitted by Gaussian curve. Solid lines with circles, squares, or triangles give approximation of error distribution. Each data set comprises 510 measurements. A) Simple visual adjustment of focal point of microscope. B) Laser-supported adjustment of focal point of microscope.

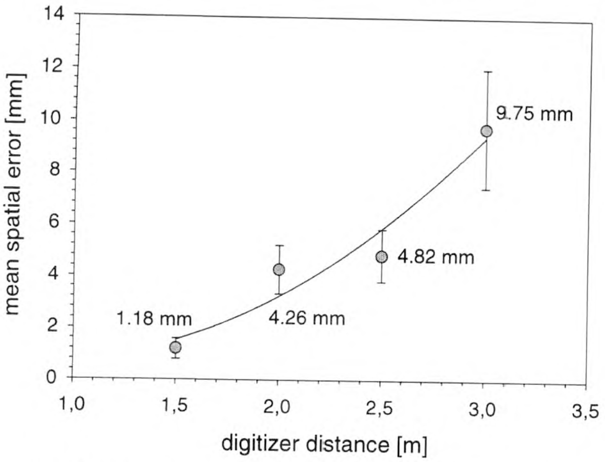


Fig 5. Dependency of mean spatial error and associated standard deviation on distance between object and digitizer. Each point provides results from 540 measurements. Focal length is 250 mm.

95th percentiles at 1.95 mm and 13.66 mm, respectively. With increasing distance, the accuracy decreased, even though the angle of the optical digitizer was optimized such that all 4 IR-LEDs of the reference panel were detected by the digitizer. Therefore, the distance of the optical digitizer from the measured object has to be controlled meticulously.

The mean spatial error decreased with increasing number of microscope IR-LEDs detected by the digitizer (Fig 6A). However, it was also dependent upon the relative position of the IR-LEDs. Even with only 3 IR-LEDs, high accuracy could be obtained when the area between the IR-LEDs was large. Therefore, with increasing area between the IR-LEDs, the spatial error decreased clearly (Fig 6B).

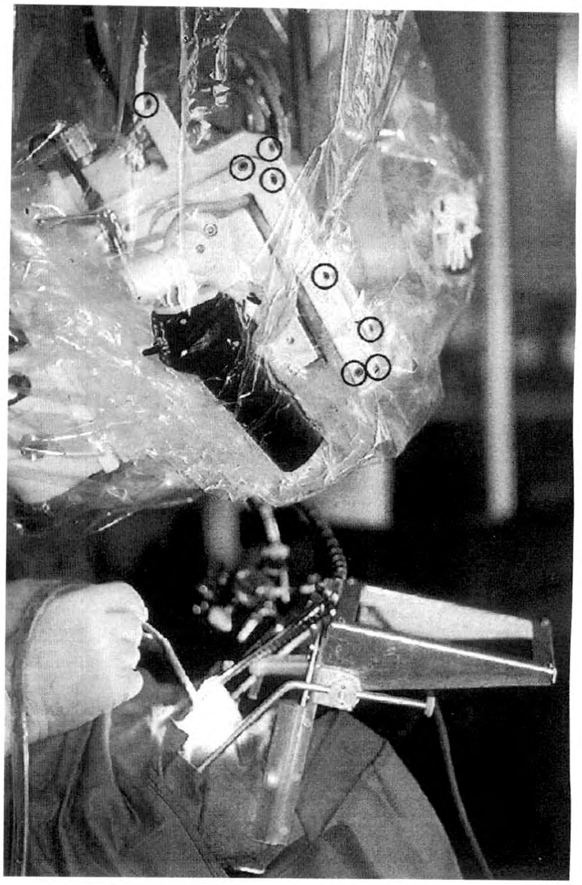


Fig 7. Intraoperative arrangement used during microscopic intranasal surgery. Face-bow with quadratic reference frame is attached to patient. Microscope is in its typical position. IR-LEDs are surrounded by circles.

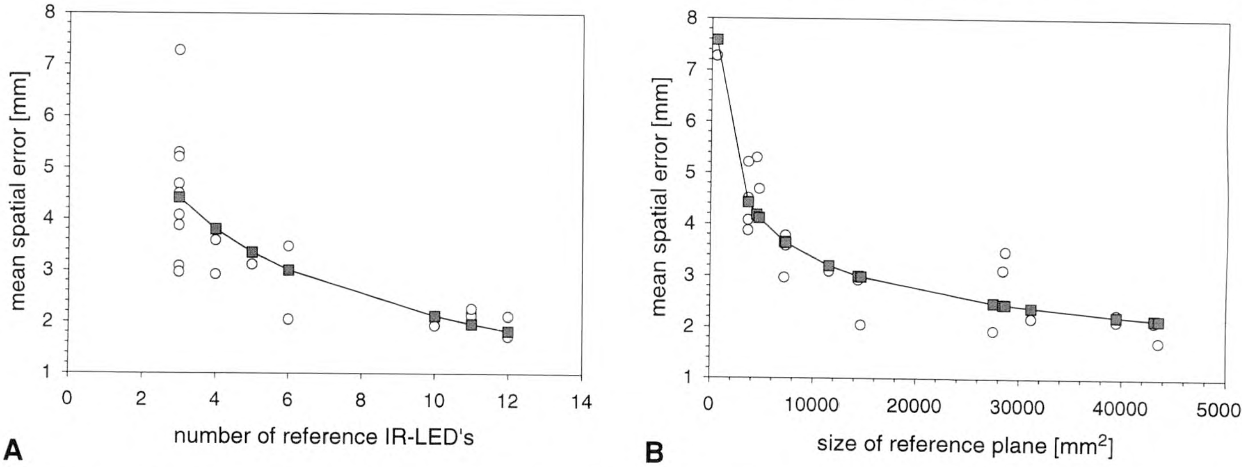


Fig 6. Dependency of mean spatial error on A) number of IR-LEDs and B) size of reference plane. Registration set is 630 measurements. Focal length is 250 mm. A) Experimental conditions were changed such that constant number of IR-LEDs could be measured with increasing area circumscribed by IR-LEDs positioned on reference frame of microscope (circles). For 3 or 6 IR-LEDs, accuracy is better when IR-LEDs are widely distributed on reference frame, ie, size of plane circumscribed is large. Overall dependency of error is shown by curve fit (squares). B) Size of plane circumscribed by IR-LEDs was varied by selecting different IR-LED positions on reference frame (circles). Also, number of IR-LEDs was considered, and dependency is indicated clearly for reference plane of approximately 5,000 mm^2 and 28,000 mm^2. Overall dependency of error is illustrated by curve fit (squares).

Patients. One important finding was that the overall accuracy of the optically locatable microscope

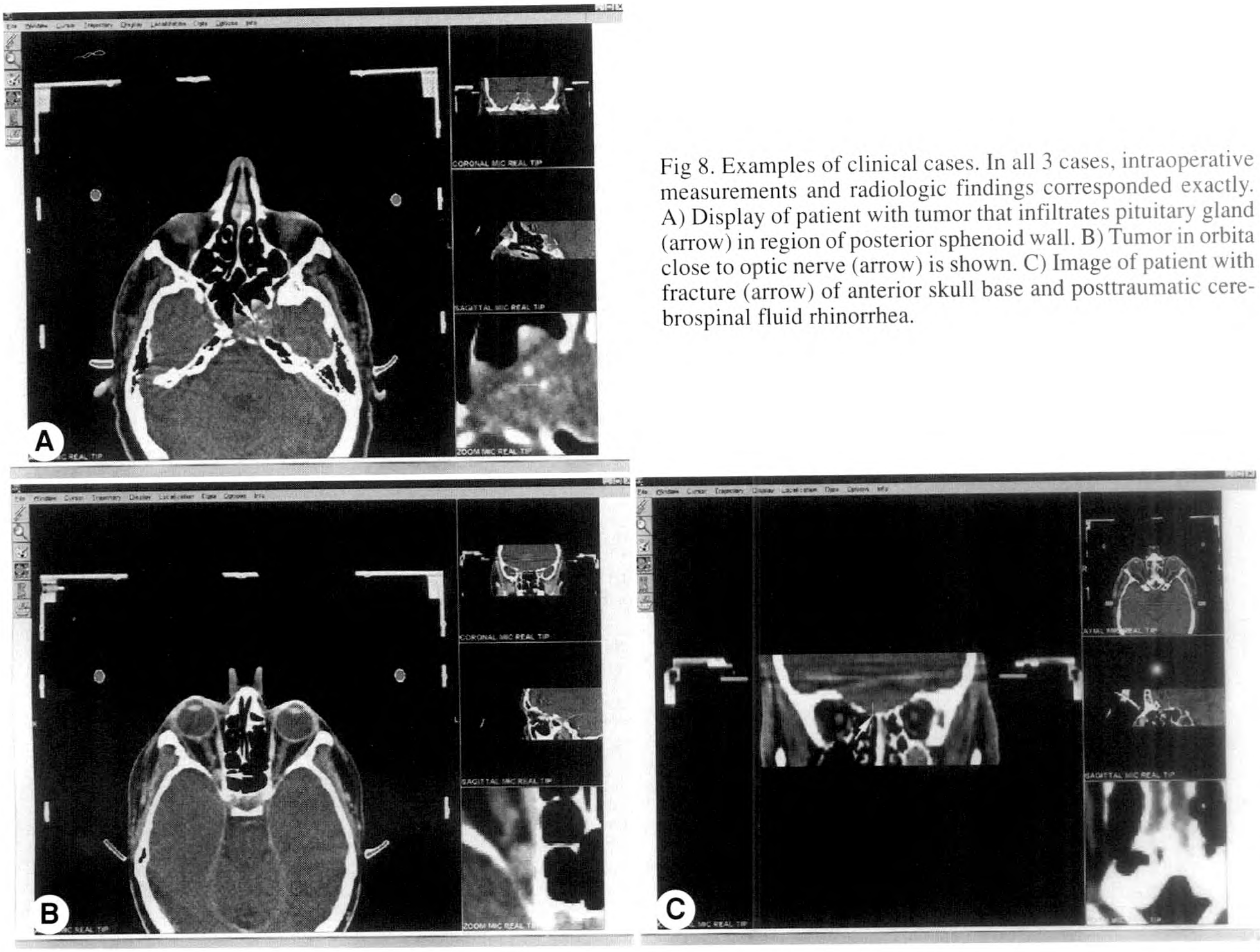


Fig 8. Examples of clinical cases. In all 3 cases, intraoperative measurements and radiologic findings corresponded exactly. A) Display of patient with tumor that infiltrates pituitary gland (arrow) in region of posterior sphenoid wall. B) Tumor in orbita close to optic nerve (arrow) is shown. C) Image of patient with fracture (arrow) of anterior skull base and posttraumatic cerebrospinal fluid rhinorrhea.

may already provide some useful intraoperative guidance and intranasal orientation for sinus surgery. Figure 7 illustrates the typical intraoperative arrangement with the reference face-bow adapted to the patient and the microscope with IR-LEDs attached. Figure 8A shows an example of a display from a patient with a tumor in the region of the posterior sphenoid wall that infiltrated the pituitary gland. After insertion of a self-retaining speculum, the anterior wall of the sphenoid was identified and removed, and a biopsy specimen of the tumor was taken. The measurements and intraoperative findings corresponded exactly. Figure 8B shows a tumor in the orbita, close to the optic nerve. It could be identified correctly and a biopsy specimen could be taken transnasally after removing the medial orbital wall covering the tumor. Figure 8C shows the image of a patient with posttraumatic cerebrospinal fluid rhinorrhea. The intraoperative localization of a preoperatively radiologically located fracture of the anterior skull base could be determined precisely during surgery.

The intraoperative measurements of the spatial error in detecting specific locations in patients had larger values in comparison with the measurements taken on the plastic skull. The mean spatial error over all locations was 2.90 ± 1.34 mm for the simple visual adjustment and 2.39 ± 1.15 mm for the laser-supported adjustment. The associated 95th percentiles were relatively large: 5.19 mm and 4.36 mm, respectively. Figure 9 illustrates the error distribution of the composite data sets taken by means of the 2 adjustment methods in patients. Although clinical accuracy may be relatively low for a single point on an anatomic structure, integrating more than a single point may enhance the surgeon's spatial orientation. Table 2 provides the statistical values of the patient measurements.

DISCUSSION

Guiding systems for intranasal sinus surgery have been proposed to support the surgeon's 3-D intraoperative orientation and to prevent complications. Different technical approaches have been used clinically, such as passive mechanical arms,[7-10] active robotic arms,[5,6] and ultrasonic,[3,11-13] electromagnetic,[14] and optical digitizing systems.[2,4,15] Currently, 3-D digitizers that are based on optical sensor technology are supposed to be the most accurate, because the systems are less affected by disturbing environmental

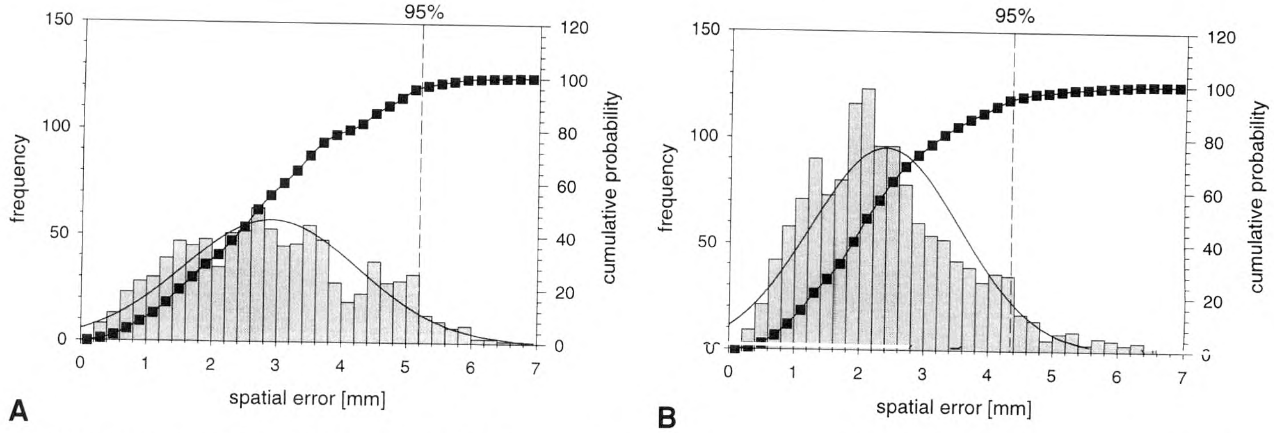


Fig 9. Distribution of spatial error and associated cumulative probability (squares) A) for simple visual adjustment of focal point in 10 patients (n = 1,000 measurements for all measured locations) and B) for laser-supported adjustment in 14 patients (n = 1,400 measurements for all measured locations). Distributions are fit by Gaussian curve (solid lines). Vertical line (dotted) indicates 95th percentile. Focal length was 250 mm.

factors than are the others.[16] Further, in contrast to mechanical arms, they allow an unobstructed view of the surgical site and a straightforward surgical procedure in the intranasal operative field. However, independent of the specific digitizing technique applied, and although relatively high technical accuracy can be reached, it remains necessary that the surgeon be familiar with the limitations of and influences on such a system.

Concerning the configuration of our system, which is mainly based on a locatable operating microscope, several possible errors have to be identified and analyzed. In principle, such errors can be classified as 1) errors that are introduced directly by the microscope, referred to as errors caused by the optical properties of the microscope, such as the method of focal point adjustment, focal length, and magnification of the lens, and 2) errors that are introduced indirectly by the microscope, referred to as errors caused by tracking properties of the microscope, such as the tracking distance to the measured object, the number of reference IR-LEDs, and the area covered by these IR-LEDs.

In general, it could be demonstrated that the spatial error of the microscope system was highly dependent on the parameters used during the targeting process. Simple visual adjustment of the focal plane by judging the visual resolution needed to obtain a clear and sharply defined image of the microscope's field of view is the most critical and error-prone step that finally determines the accuracy of targeting. The reason for the lower error rate with the laser-supported method is that the superpositioning of the 2 crossing gleaming lasers indicates the focus and decreases the influence of the individual visual adaptation of the surgeon. Moreover, the overlay of the laser-light marks in the field of view of the microscope allows a clear assessment of the focus even when lenses with a higher depth of focus are used. For a focal length of 350 mm, the error was reduced from 2.54 ± 0.71 mm to 1.79 ± 0.46 mm. That corresponds to a relative accuracy improvement of approximately 30%. Moreover, the error dependency on the focal length shows that the mean spatial error is increased from 1.18 ± 0.39 mm for a focal length of 250 mm to 1.79 ± 0.64 mm for a focal length of 350 mm. The increase can be mainly attributed to a higher depth of focus and a reduced magnification of up to 71.5% for lenses with a higher focal length, which make it more difficult to determine the focal point exactly, even with the laser-supported adjustment.

TABLE 2. SUMMARY OF STATISTICAL VALUES FOR VISUAL AND LASER-SUPPORTED ADJUSTMENT OF FOCAL POINT IN PATIENTS

	Simple Visual Adjustment Error (mm)	*Laser-Supported Adjustment Error (mm)*
Mean	2.90	2.39
SD	1.34	1.15
SE	0.04	0.03
95th Percentile	5.19	4.36
Maximal value	6.79	6.54

Focal length of lens was 250 mm.

Other approaches[5,17] that use an automatic measurement to control the distance between the principal plane of the lens and a structure in the operative field intersected by the microscope's optical trajectory may provide more objective and accurate values, because the measurement is performed independent of the focal length. Additionally, automatic measurement could speed up the entire targeting process and reduce errors that result from individual refraction anomalies, magnification, and depth resolution. However, no such system has been tested in detail for accuracy, and no clinical data are available on such systems' application and applicability in intranasal sinus surgery.

The space in which the microscope and the patient's head can be moved relative to each other is limited to a small working area, because a close geometric relationship is necessary to obtain a good view of the deep and narrow operative field of the nasal cavity. Therefore, the linear distance movement between the digitizer and the skull model may have a major impact on accuracy. The results indicate clearly that for reasonable mean accuracy, the digitizer has to be close to the measured object. This influence has to be strongly controlled for, because accuracy may decrease sharply by a factor of about 4 or more if the distance of the digitizer from the operative field is increased to a range between 2.0 and 3.0 m.

A further factor that contributes significantly to the accuracy of the targeting process is the number of detected IR-LEDs that are attached to the microscope. However, the error is not a single function of the number of IR-LEDs. The error pattern shows that the area circumscribed by those IR-LEDs is also a major factor that affects the accuracy. As demonstrated, the mean spatial error decreased clearly with the increasing number of IR-LEDs detected and the increasing area between these IR-LEDs, but even a small number of spatially widely distributed IR-LEDs may provide a high accuracy. Therefore, the number and geometric arrangement of IR-LEDs have to be considered as important clinical features that influence the accuracy and reliability of intraoperative decision making. It seems obvious that the arrangement of the IR-LEDs as close as possible to the lens reduces the error because the impact of rotational and translational errors introduced during position measurement of the IR-LEDs on digitizing is then relatively small.

For application during surgery, we optimized the arrangement of our system according to the results drawn from the skull model experiments. A mean spatial error of 2.39 ± 1.15 mm for the laser-supported adjustment of the focal point is a reasonable value for microscopic guidance at this early stage of our study. Such accuracy is encouraging when we take into consideration that a noninvasive procedure is performed for the initial patient-to-image registration and that the resolution of the CT image in the third dimension is only 2 mm because of slice thickness and distance. Moreover, intraoperative decision making currently is not based on a single point localization trail, but on the spatial relation of several measured points in the region of interest of the operative field. It has to be admitted that overall accuracy is actually still less than with optically locatable surgical instruments as described earlier by the authors,[2] who found a mean spatial error of 1.56 mm ± 0.76 mm intraoperatively. However, if a clinically meaningful 3-D superpositioning of preoperatively acquired image data and the intraoperative site of disease as described by Edwards et al[4] is to be widely clinically applied, then the disadvantages of today's locatable microscopes in comparison with locatable surgical instruments may be counterbalanced. The surgeon's eye could perform the fusion of a 3-D image with surface contours with a high degree of accuracy. Such a possibility would also make the cumbersome readjustments of the system unnecessary when approaching and targeting a new structure. For image-guided intranasal sinus surgery, a reliable and meaningful 3-D transparent image that is superpositioned over anatomic structures would seem to be the ideal solution from our surgical viewpoint today.

ACKNOWLEDGMENT — The authors thank F. P. Harris, PhD, for reading the manuscript and for her editorial assistance.

REFERENCES

1. Westermann B, Hauser R. Non-invasive 3-D patient registration for image-guided skull base surgery. Comput Graph 1996;20:793-9.
2. Hauser R, Westermann B, Probst R. Non-invasive tracking of patient's head movements during computer-assisted intranasal microscopic surgery. Laryngoscope 1997;107:491-9.
3. Roberts DW, Strohbehn JW, Hatch JF, Murray W, Kettenberger H. A frameless stereotaxic integration of computerized tomographic imaging and the operating microscope. J Neurosurg 1986;65:545-9.
4. Edwards PJ, Hawkes DJ, Hill DLG, et al. Augmentation of reality using an operating microscope for otolaryngology and neurosurgical guidance. J Image Guided Surg 1995;1:172-8.
5. Luber J, Mackevics A. Multiple Co-Ordinate Manipulator (MKM). A computer-assisted microscope. Computer Assisted Radiology. Proceedings of the International Symposium on Computer and Communication Systems for Image Guided Diagnosis and Therapy. CAR '95 Berlin, June 1995:1121-5.
6. Giorgi C, Eisenberg H, Costi G, Gallo E, Garibotto G, Casolino DS. Robot-assisted microscope for neurosurgery. J Image Guided Surg 1995;1:158-63.
7. Mösges R, Schlöndorff G. A new imaging method for intraoperative therapy control in skull-base surgery. Neurosurg Rev 1988;11:245-7.
8. Anon JB, Lipman SP, Oppenheim D, Halt RA. Computer-assisted endoscopic sinus surgery. Laryngoscope 1994;104:901-5.
9. Kelly PJ, Alker GJ, Goerss S. Computer-assisted stereotactic laser microsurgery for treatment of intracranial neoplasms.

Neurosurgery 1982;10:324-31.

10. Zinreich SJ, Tebo SA, Long DM, et al. Frameless stereotaxic integration of CT imaging data: accuracy and initial applications. Radiology 1993;188:735-42.

11. Nitsche N, Hilbert M, Strasser G, Tummler HP, Arnold W. Einsatz eines berührungsfreien computergestützten Orientierungssystems bei Nasennebenhöhlenoperationen. I. Technische Grundlagen der Sonarstereometrie. Otorhinolaryngol Nova 1993;3:57-64.

12. Nitsche N, Hilbert M, Strasser G, Schulz HJ, Wunderlich A, Arnold W. Einsatz eines berührungsfreien computergestützten Orientierungssystems bei Nasennebenhöhlenoperationen. II. Anatomische Studien und erste klinische Erfahrungen. Otorhinolaryngol Nova 1993;3:173-9.

13. Reinhardt HF, Horstmann GA, Gratzl O. Sonic stereometry in microsurgical procedures for deep-seated brain tumors and vascular malformations. Neurosurgery 1993;32:51-7.

14. Gunkel AR, Freysinger W, Thumfart WF, Pototschnig C. Complete sphenoethmoidectomy and computer-assisted surgery. Acta Otorhinolaryngol Belg 1995;49:257-61.

15. Tebo SA, Leopold DA, Long DM, Zinreich SJ. An optical digitizer for frameless stereotactic surgery. IEEE Comput Graph Appl 1996;16:55-64.

16. Bucholz RD, Smith KR, Henderson JM, McDurmont L, Schulz D. Intraoperative localization using a three dimensional optical digitizer. SPIE Proc Ser 1993;1894:311-22.

17. Westermann B, Trippel M, Reinhardt H. Optically-navigable operating microscope for image-guided surgery. Minim Invasive Neurosurg 1995;38:112-6.

≈

RECENT ADVANCES IN OTITIS MEDIA

The 7th International Symposium on Recent Advances in Otitis Media will be held June 1-5, 1999, in Fort Lauderdale, Florida. For information, contact David J. Lim, MD, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057.

≈

FUNCTIONAL AESTHETIC NASAL SURGERY

The 17th International Course in Functional Aesthetic Nasal Surgery will be held in English, June 15-18, 1999, in Utrecht, the Netherlands. For information, contact Ms. T. Kortleve, Dept of ORL, University Hospital Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands; telephone +31-30-2506645; fax +31-30-2541922; e-mail t.kortleve@kmb.azu.nl.

Ann Otol Rhinol Laryngol 108:1999

MANOMETRIC STUDY OF PARANASAL SINUS MUCOCELES

ERIK S. KASS, MD
BETHESDA, MARYLAND

RICHARD L. FABIAN, MD
BOSTON, MASSACHUSETTS

WILLIAM W. MONTGOMERY, MD
BOSTON, MASSACHUSETTS

A paranasal sinus mucocele is a chronic cystlike lesion characterized by slowly progressive remodeling and expansion of the surrounding osseous walls. If left untreated, it may cause significant facial deformity, ophthalmic disturbances, and, in the worst instance, intracranial complications. According to a review of the literature, there is a long-held view that positive pressure exists within paranasal sinus mucoceles; however, to our knowledge, pressure measurements have not been recorded in humans. In this study, pressure measurements were taken of 4 paranasal sinus mucoceles by means of an 18-gauge needle probe and an amplified pressure transducer. The average value was +15 cm H_2O with a range of +4 to +39 cm H_2O. This study confirms the long-standing assumption that positive pressure exists within paranasal sinus mucoceles. The magnitude of the pressure was comparable to that which was found to be associated with bone resorption in several previously published studies. Further studies are needed to determine whether positive pressure and osseous remodeling are causally related in this condition.

KEY WORDS — manometry, paranasal sinus mucocele.

INTRODUCTION

A paranasal sinus mucocele is defined as a chronic cystlike lesion that contains sinus secretions, desquamation, and inflammation.[1] It is histologically distinguished from a retention cyst by the location of accumulated products superficial to the mucosa.[1] Clinically, it is characterized by a slow outward deformation of the osseous walls of the sinus.[1,2] A 15-year retrospective study of 110 cases of paranasal sinus mucoceles diagnosed at the Massachusetts Eye and Ear Infirmary showed that the most commonly involved sinus was the frontal (40%), followed by the ethmoid (27%), supraorbital ethmoid (15%), sphenoid (8%), and maxillary (5%). Multiple sinus involvement was the least common and occurred in 5 cases (Fig 1).

Development of a frontal sinus mucocele is thought to occur as a result of blockage of the nasofrontal duct.[1-3] The cause of this blockage may be attributed to traumatic fracture through the duct.[3,4] Expansion of a frontal sinus mucocele may eventually lead to forward, downward, and lateral displacement of the ipsilateral eye and deformity of the forehead.[1,2,5] Infection of a mucocele results in the development of a pyocele.[1,2] A pyocele accelerates bony wall erosion and, if left untreated, may result in catastrophic intracranial or intraorbital complications.[1,3,6]

There is speculation regarding the pathogenesis of mucoceles.[7-9] The inner aspect of the osseous walls of a mucocele typically has a concave appearance on x-ray.[2,10] This expansile quality has led to a long-standing assumption that chronic positive pressure exists within the enclosed space of a mucocele.[1,6,7] Some authors have suggested that bacterial antigens at the interface between the mucocele and the surrounding osseous walls, rather than positive pressure, result in bone erosion.[8,9] Static pressure within mucoceles has not been measured in humans; however, positive pressure has been measured within experimentally induced mucoceles in a feline model.[11] Pressure measurements in 4 cats averaged +17.1 cm

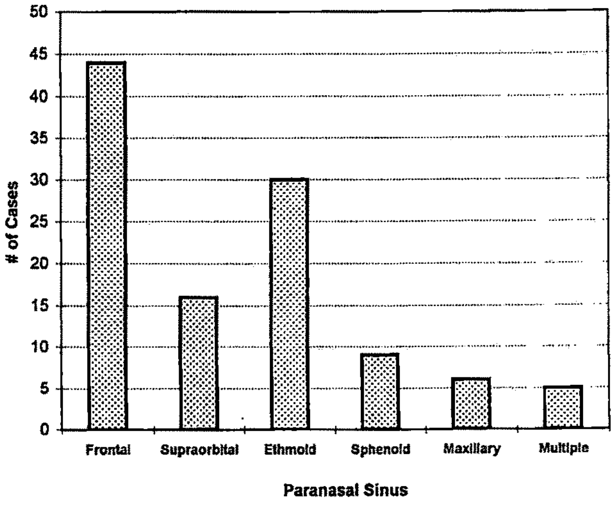


Fig 1. Distribution of paranasal sinus mucoceles in 15-year retrospective study of 110 cases.

From the Department of Otology and Laryngology, Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

CORRESPONDENCE — Erik S. Kass, MD, National Institutes of Health, Building 10, Room 8B07, 10 Center Dr MSC 1750, Bethesda, MD 20892-1750.

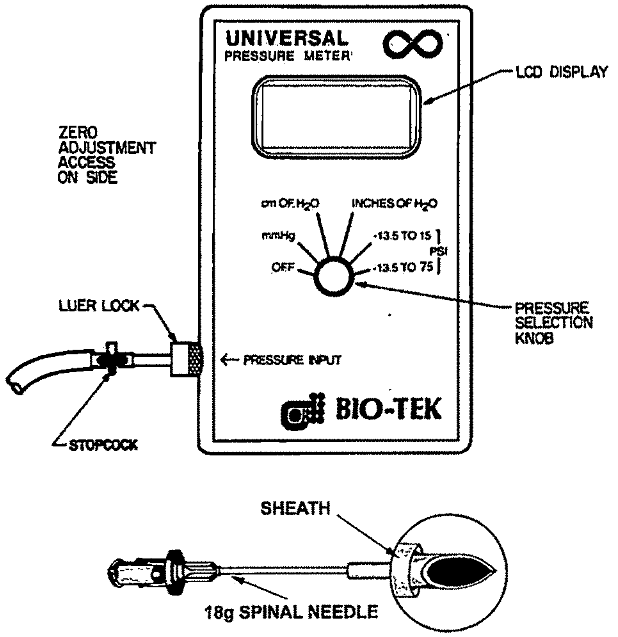


Fig 2. Electronic pressure transducer amplifier unit (Bio-tek Instruments Inc, DPM-II) used to record pressure. Input port of pressure-transducing unit was connected to 18-gauge spinal needle via 120-cm section of standard pressure tubing. Cut section of butterfly angiocatheter tubing was snugly fitted to within 4 mm of needle's tip, to serve as depth limitation sheath. Unit was adjusted to 0 at atmospheric pressure before each recording.

H2O.[11] In the present study, static pressure measurements were taken in 3 adults with spontaneously occurring paranasal sinus mucoceles.

PATIENTS AND METHODS

All patients in this study had preoperative computed tomography (CT) scans of the paranasal sinuses in the axial and coronal planes. Patients were divided into experimental and control groups, and static pressure measurements were made of the paranasal sinuses in all patients. The experimental group comprised 3 adults found by CT to have paranasal sinus mucoceles. The control group comprised 5 adults found by CT to have chronic sinusitis. Informed consent was obtained from all patients, and all measurements were taken intraoperatively with the patients under general inhalation anesthesia without nitrous oxide.

Manometric recordings were made in centimeters of water pressure with an electronic pressure-sensitive transducer and amplifier unit (Bio-tek Instruments Inc, Universal Pressure Meter model DPM-II; Fig 2). The input port of the pressure-transducing unit was connected by a Luer lock adapter to a 120-cm section of standard pressure tubing (model 50-P248, Baxter Inc) and was calibrated to a pressure analyzer (model GSI 33, Grason-Stadler, Inc). The pressure transducer unit was set to 0 at atmospheric pressure before each reading was taken. Measurements were taken with an 18-gauge spinal needle fitted with a plastic depth limitation guard. The needle was connected by a Luer lock adapter to the distal end of the pressure tubing.

The distal portion of the needle was coated with a film of ointment up to, but not including, the tip to further ensure that a closed system was maintained as the needle entered the sinus. Following penetration through the wall of the mucocele, the needle was advanced a total distance of approximately 4 mm to ensure complete entry of the beveled tip. In the experimental group, entry was made into the mucocele at a site of bony dehiscence. In the control group, entry was made into the maxillary sinus via the membranous fontanel under endoscopic guidance, as previously described.[12] Pressure readings were not recorded until steady state was achieved.

RESULTS

The first patient had a mucocele of the left frontal sinus, and the second had one of the left maxillary sinus. The third patient had mucoceles of the right supraorbital ethmoid sinus and left sphenoid sinus. Axial and coronal CT scans demonstrated expansile lesions containing fluid. The inner aspect of the bony wall surrounding these lesions was concave, thinned, and partially dehiscent (Fig 3). Measurements of the maximum dimension of each mucocele were taken from the CT scan and ranged from 2.4 to 4 cm.

Intraoperative findings confirmed the presence of thick and turbid secretions within the mucoceles. Areas of osseous wall expansion with eggshell-thin and partially dehiscent bone were seen. There was mild to moderate mucosal thickening. Pressure measurements within the mucoceles ranged from +4 to +39 cm H2O with a mean of +15 cm H2O and a standard deviation of 16.6 cm H2O (see Table). Pressure measurements were isobaric for all patients in the control group.

The frontal mucocele was treated with an osteoplastic frontal sinus obliteration utilizing abdominal adipose tissue. The supraorbital ethmoid mucocele was treated with a Lynch frontoethmoidectomy. In the case of the sphenoid mucocele, a large sphenoidotomy was performed endoscopically. A canine fossa maxillotomy and middle meatal antrostomy were done for the maxillary sinus mucocele. In each case, areas of diseased mucosa were stripped. The early postoperative course for all patients was uneventful.

Histopathology showed mild chronic inflammatory changes in the mucosa with mucus retention and areas of submucosal fibrosis. There was osteoclastic rimming of lamellar bone fragments consistent

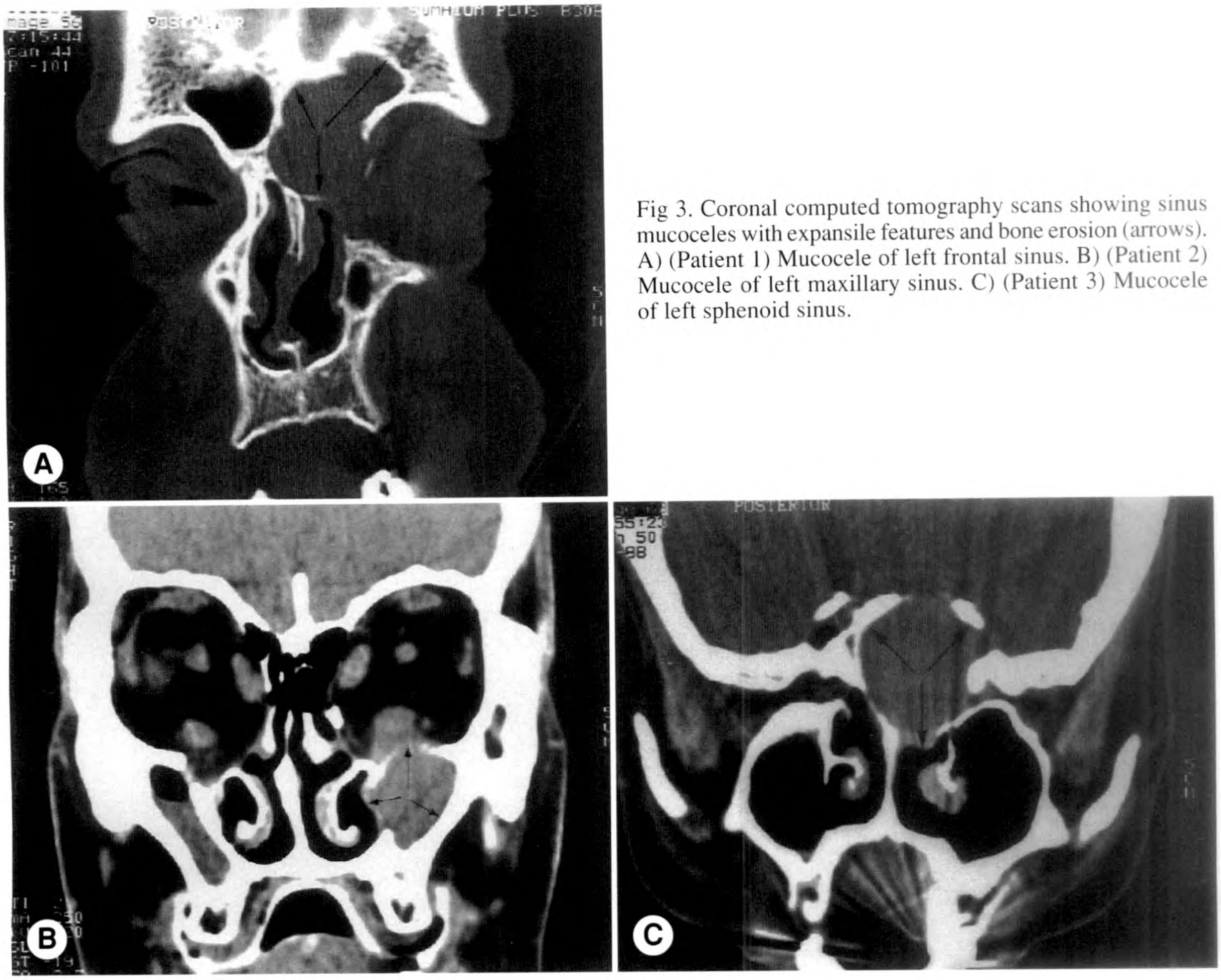


Fig 3. Coronal computed tomography scans showing sinus mucoceles with expansile features and bone erosion (arrows). A) (Patient 1) Mucocele of left frontal sinus. B) (Patient 2) Mucocele of left maxillary sinus. C) (Patient 3) Mucocele of left sphenoid sinus.

with active bone remodeling.

DISCUSSION

The etiology and pathogenesis of paranasal sinus mucoceles has been the subject of interest and debate among otolaryngologists for over a century.[2] Much of the fascination with mucoceles stems from their expansile nature, which can often lead to impressive osseous deformation.[2] Ostial occlusion is thought to be a necessary predisposing factor in their development,[3,7] but this factor does not seem to be sufficient, since sinus occlusion can also result in chronic sinus atelectasis.[13]

MANOMETRIC VALUES IN PATIENTS WITH PARANASAL SINUS MUCOCELES

Patient No.	*Age (y)*	*Sex*	*Paranasal Sinus*	*Size (mm)*	*Pressure (cm H_2O)*
1	58	M	Left frontal	38	+4
2	42	F	Left maxillary	24	+39
3	80	F	Right ethmoid	32	+13
			Left sphenoid	40	+4

The pathway by which osteoclasts and osteoblasts are stimulated to remodel the osseous walls of an expanding mucocele is not known with certainty.[9] Bone resorptive factors have been found at the interface between the mucocele and its osseous walls.[8,9] Cytokine release by local inflammatory cells stimulates the secretion of prostaglandin E2 (PGE2) and collagenase by fibroblasts. The end result of this cascade of events is bone resorption.[9,14,15]

Lund and Milroy[9] postulate that bone resorption is principally incited by bacterial antigens that stimulate release of interleukin-1 (IL-1) and other cytokines by mononuclear cells adjacent to periosteum. Positive pressure across the mucoperiosteum is known to incite bone resorption directly, through osteoclast stimulation, and indirectly, through cytokine release.[14-19] Interleukin-1 is known to be released by stimulated fibroblasts, and positive pressure has been shown to result in PGE2 synthesis and bone resorption.[15-18]

In this study, the average pressure measurement compared closely with the mean value recorded in cats with experimentally induced mucoceles.[11] It was similar in magnitude to the average pressure recorded in patients with osseous deformity secondary to chronic maxillary atelectasis.[12] The magnitude of the pressure was also in the same range as that found to induce bone resorption in the middle ear of rats[19] and was more than the mean pressure measured in bone-eroding cholesteatomata.[20] Overall, the results from this study suggest that sufficient pressure was present within each mucocele to stimulate osseous remodeling.

The often smooth and evenly contoured concavity of the inner osseous walls of a mucocele implies that uniform net bone resorption may be occurring along the inner periosteum. Fluid under pressure within the enclosed space of a mucocele would distribute force evenly along the periosteum and would therefore be expected to uniformly stimulate bone remodeling. Bone resorption due to infection typically lacks this uniformity and commonly shows a moth-eaten or scalloped appearance, as is seen in osteomyelitis.[21,22]

Mucoceles and sinus atelectasis may represent opposite extremes along a continuum of diseases that result from complete ostial occlusion of a paranasal sinus. What determines which entity will develop in response to complete obstruction is not known, but may include the constitutive cellular makeup and metabolic functioning of the host's epithelial lining. Of importance, it is the overall response of the host's epithelial lining that determines whether the sinus will be in a net absorptive or secretory state. In either instance, inflammation would be expected to play a synergistic role in osseous remodeling.[22]

CONCLUSION

This study confirms the long-standing assumption that positive pressure exists within paranasal sinus mucoceles. The magnitude of the pressure was comparable to that found to be associated with bone resorption in several previously published studies. Further studies are needed to determine whether positive pressure and osseous remodeling are causally related in paranasal mucoceles.

ACKNOWLEDGMENTS — We thank Salah Salman, MD, for his editorial assistance. We also thank Kenneth R. Pellegrino, CBET, and Christopher Halpin, PhD, for their technical assistance. Finally, we would like to express our gratitude to Michael P. Joseph, MD, and to Neil Bhattacharyya, MD, for their cooperation.

REFERENCES

1. Schuknecht HF, Lindsay JR. Benign cysts of the paranasal sinuses. Arch Otolaryngol 1949;49:609-30.

2. English GM. Otolaryngology: a textbook. Philadelphia, Pa: JB Lippincott–Raven Press, 1993.

3. Hybels RL, Newman MH. Posterior table fractures of the frontal sinus. I. An experimental study. Laryngoscope 1977;87:171-9.

4. Hardy JM, Montgomery WW. Osteoplastic frontal sinusotomy. An analysis of 250 operations. Ann Otol Rhinol Laryngol 1976;85:523-32.

5. Mortada A. Exophthalmos and posterior frontocele with fibrous wall on orbital side. Am J Ophthalmol 1971;72:701-4.

6. Stiernberg CM, Bailey BJ, Calhoun KH, Quinn FB. Management of invasive fronto-ethmoidal sinus mucoceles. Arch Otolaryngol Head Neck Surg 1986;112:1060-3.

7. Batsakis JG. Tumors of the head and neck. Baltimore, Md: Wilkins and Wilkins, 1980.

8. Lund VJ. Anatomical considerations in the aetiology of fronto-ethmoidal mucoceles. Rhinology 1987;25:83-8.

9. Lund VJ, Milroy CM. Fronto-ethmoidal mucoceles: a histopathological analysis. J Laryngol Otol 1991;105:921-3.

10. Weber AL. Inflammatory diseases of the paranasal sinuses and mucoceles. Otolaryngol Clin North Am 1988;21:421-37.

11. Fenton WH, Donald MD, Carlton W. The pressure exerted by mucoceles in the frontal sinus. Arch Otolaryngol Head Neck Surg 1990;116:836-40.

12. Kass ES, Salman S, Montgomery WW. Manometric study of complete ostial occlusion in chronic maxillary atelectasis. Laryngoscope 1996;106:1255-8.

13. Kass ES, Salman S, Rubin PAD, Weber AL, Montgomery WW. Chronic maxillary atelectasis. Ann Otol Rhinol Laryngol 1997;106:109-16.

14. Lorenzo JA. The role of cytokines in the regulation of local bone resorption. Crit Rev Immunol 1991;11:195-213.

15. Newton RC, Covington M. The activation of human fibroblast prostaglandin E production by interleukin 1. Cell Immunol 1987;110:338-49.

16. Binderman I, Zor U, Kaye AM, Shimshoni Z, Harell A, Somjen D. The transduction of mechanical force into biochemical events in bone cells may involve activation of phospholipase A2. Calcif Tissue Int 1988;42:261-6.

17. Imamura K, Ozawa H, Takatoshi H, et al. Continuously applied compression pressure induces bone resorption by a mechanism involving prostaglandin E2 synthesis. J Cell Physiol 1990;144:222-8.

18. Elias JA, Reynolds MM, Kotloff RM, Kern JA. Fibroblast interleukin 1 beta: synergistic stimulation by recombinant interleukin 1 and tumor necrosis factor and posttranscriptional regulation. Proc Natl Acad Sci U S A 1989;86:6171-5.

19. Huang C, Yi Z-X, Yuan Q-G, Abramson M. A morphometric study of the effects of pressure on bone resorption in the middle ear of rats. Am J Otol 1990;11:39-43.

20. Orisek BS, Chole RA. Pressures exerted by experimental cholesteatomas. Arch Otolaryngol Head Neck Surg 1987;113:386-91.

21. Wenig BM. Atlas of head and neck pathology. Philadelphia, Pa: WB Saunders, 1993.

22. Meininger GR, Police P, Niparko JK. Chronic osteomyelitis of the skull base (OSB). Arch Otolaryngol Head Neck Surg 1997;123:351-2.

RADIOGRAPHIC EVALUATION OF CHILDREN WITH NASOPHARYNGEAL OBSTRUCTION DUE TO THE ADENOID

YUSUF K. KEMALOGLU, MD
NEBIL GOKSU, MD
ERDOGAN INAL, MD
NECMETTIN AKYILDIZ, MD
ANKARA, TURKEY

The adenoidal-nasopharyngeal ratio (ANR) was proposed as a convenient and practical method to evaluate adenoidal enlargement. We analyzed cephalometric radiographs of 150 children divided into 6 subgroups according to clinical assessment (possible adenoidectomy candidates [PACs] and controls) and age. Our purpose was to investigate the predictive reliability of different ANRs calculated on the same reference line. Each of the ANRs described in this study presented statistically significant differences between PACs and control groups, and highly significant correlations with clinical symptoms of nasal obstruction. Further, the mean adenoidal depth was significantly larger in PACs than in normals, and it was found that the adenoidal depth in PACs did not show a significant decrement with age, in contrast to normals. On the other hand, although nasopharyngeal depth was not different between PACs and normals, an age-dependent increment was observed in PACs, in contrast to normals. Thus, it could be said that the ANR is a more reliable method for determining whether adenoidal hyperplasia is clinically significant or not, rather than the size of the adenoid or nasopharynx.

KEY WORDS — adenoid, airway obstruction, cephalometry, maxillofacial development, nasal obstruction, nasopharynx, radiology, sleep apnea, snoring.

INTRODUCTION

Adenotonsillectomy is one of the most frequent procedures in all of surgery. In determining whether adenotonsillar enlargement is sufficient to be clinically significant, the physician typically relies on the physical examination and history. Physical examination, however, provides little information about the size of the adenoid, although enlarged tonsils may be proved easily. Several radiologic techniques have been proposed to confirm the decision for adenoidectomy.[1-3] However, their use in routine daily practice has not been popular, since the interpretation of radiographs has varied from author to author. Moreover, some of these techniques are expensive and unavailable in many medical centers.

The adenoidal-nasopharyngeal ratio (ANR) was first proposed as a predictive method by Fujioka et al,[4] but Linder-Aronson[5] used a similar ratio of adenoidal and nasopharyngeal depths as a parameter in his detailed investigation, and emphasized the importance of this ratio in nasal obstruction symptomatology due to adenoidal tissue before Fujioka et al. The authors who used ANR subsequently indicated that it was a practical and convenient method having a high correlation with degree of symptoms, since it appreciates the size of the adenoidal mass and the size of the nasopharyngeal space, together.[6,7] In a previous study, we supported this notion, as well.[8]

Another point under discussion in the concept of nasopharyngeal obstruction due to the adenoid is the size of the nasopharynx. It is well known that both the nasopharyngeal skeleton and nasopharyngeal lymphoid tissue have their own age-dependent developmental patterns,[9-15] and some previous investigators claimed that a small nasopharyngeal capacity had more of an effect on nasal obstruction caused by the adenoid than did a large adenoid.[5,11,13,16]

Thus, the present study set out, first, to assess the predictive reliability of different ANRs in determining candidacy for adenoidectomy according to age and, further, to investigate the separate effects of adenoidal and nasopharyngeal depths on nasal obstruction by the adenoid.

MATERIALS AND METHODS

Subjects. One hundred fifty children (66 girls and 84 boys) were divided into 2 main groups according to clinical assessment, and then into 3 age subgroups in each, for this analysis. The age groups and mean ages are presented in Table 1. The mean age for all subjects was 83.39 months.

Clinical Assessment. In each subject, clinical assessment was made by 2 observers (first author of this study and another otolaryngological surgeon). Subjects who had septal deviation, a history of allergic rhinitis, or poor general condition were ex-

---

From the Department of Otorhinolaryngology, Gazi University School of Medicine, Ankara, Turkey.
CORRESPONDENCE — Yusuf K. Kemaloglu, MD, Yalim sokak 2/13, Kavaklidere, Ankara, 06660 Turkey.

TABLE 1. MEAN AGES AND NUMBERS OF SUBJECTS IN EACH GROUP

Age Groups	Clinical Groups (CNOS)	No.	Mean Age ± SD (mo)
48-71 mo	A-I (0 or 1)	25	60.60 ± 7.11
	A-II (2 or 3)	25	59.52 ± 7.38
72-95 mo	B-I (0 or 1)	25	82.52 ± 0.49
	B-II (2 or 3)	25	81.08 ± 6.68
96-120 mo	C-I (0 or 1)	25	106.32 ± 8.07
	C-II (2 or 3)	25	110.28 ± 9.16

CNOS — clinical nasal obstruction score (0 — no adenoidal mass; 1 — slight or suspicious adenoidal mass; 2 — moderate adenoidal mass; 3 — extreme adenoidal mass).

cluded from this study, and sinusitis was treated before clinical assessment.

TABLE 2. REFERENCE POINTS, LINES, AND RATIOS USED FOR RADIOLOGIC ASSESSMENT

	Reference points
U1	Intersection between adenoidal shadow and PSyL
U1'	Intersection between nasopharyngeal surface of spheno-occipital bone and PSyL
U2	Nearest adenoidal point to P
U2'	Intersection between nasopharyngeal surface of spheno-occipital bone and PU2L
U3	Intersection point between adenoidal shadow and PBaL
Ba	Basion; most posteroinferior point on anterior margin of foramen magnum
P	Posterior nasal spine; most posterior point of hard palate
Sy	Posterosuperior point of sphenobasioccipital synchondrosis
	Reference lines
PU2L	Line through P and U2
PBaL	Line through P and Ba
PSyL	Line through P and Sy
	Ratios
ANR-Sy	Ratio of distance between U1 and U1' to distance between P and U1'
ANR-U2	Ratio of distance between U2 and U2' to distance between P and U2'
ANR-Ba	Ratio of distance between U3 and Ba to distance between P and Ba

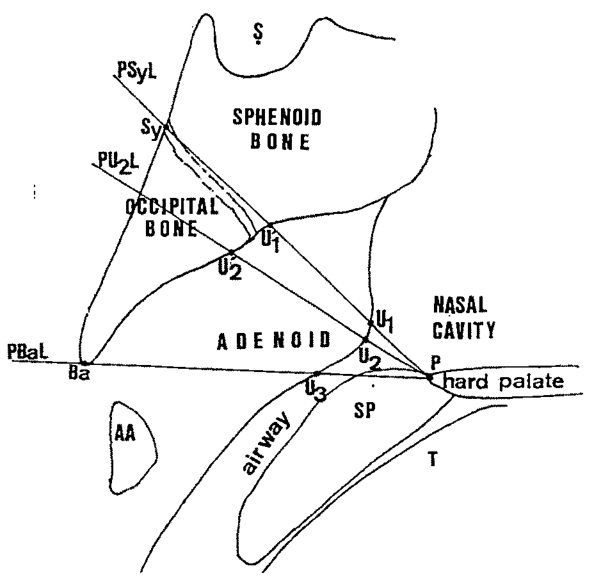


Fig 1. Reference points and lines on lateral cephalography (AA — most anterior point of atlas; U1, U2, and U3 — adenoidal points described in Table 2; U1', U2', Ba, and Sy — cranial base points described in Table 2; PSyL, PU2L, and PBaL — lines described in Table 2; S — sella; SP — soft palate; T — tongue). For calculation of adenoidal-nasopharyngeal ratios (ANRs): first, P-U1', P-U2', and P-Ba are measured as nasopharyngeal depths, and U1-U1', U2-U2', and U3-Ba, as adenoidal depths. Subsequently, each ANR is simply calculated as adenoidal depth divided by nasopharyngeal depth on same line.

Nasal breathing was evaluated according to the presence of snoring, mouth breathing, and sleep apnea in all groups. For this purpose, the mothers were asked about snoring, mouth breathing, and sleep apnea, and observers scored the answers as 1 (present) or 0 (absent). Subsequently, the scores of each child were added, and the clinical nasal obstruction score (CNOS) of each child was determined. Then, the subjects were grouped according to CNOS, as follows: 0, no adenoidal mass; 1, slight or suspicious adenoidal mass; 2, moderate adenoidal mass; or 3, extreme adenoidal mass. Cases in which both observers reached a consensus were included in the study. The children with a CNOS of 0 or 1 were considered the control group, and those with a CNOS of 2 or 3 were considered as possible adenoidectomy candidates (PACs). Each age group included 25 control subjects and 25 PACs (Table 1).

Radiologic Assessment. Lateral cephalographs were obtained with the subject in the erect position, with the teeth in occlusion and the lips in repose during film exposure. The head was fixed with a cephalostat, which holds the head in a fixed and reproducible position. Stabilization is achieved by a pair of ear rods that enter the external auditory meatus and minimize changes in head position. A third point of fixation is achieved with a rod that rests passively on the soft tissue covering the inferior orbital rim or nasopharyngeal suture. This prevents head rotation along the sagittal plane. In this study, the tube-head distance and the head-cassette distance were 1.52 cm and 12 cm, respectively. The exposures were made at 65 to 70 kV with an exposure time of 0.6 second.

By using the reference points and lines presented in Table 2 and Fig 1, we separately measured 3 adenoidal and 3 nasopharyngeal depths. The 3 ANRs (ANR-Sy, ANR-U2, and ANR-Ba) were calculated as the ratio of adenoidal depth to nasopharyngeal

TABLE 3. STATISTICAL ANALYSES OF ANRs OF NORMAL SUBJECTS AND ADENOIDECTOMY CANDIDATES (*T*-TEST)

ANR	*Groups*	*Average*	*SD*	*No.*	t
ANR-Sy	A-I	0.50	0.10	25	7.33*
	A-II	0.68	0.08	25	
	B-I	0.40	0.10	25	6.26*
	B-II	0.63	0.15	25	
	C-I	0.45	0.65	25	7.14*
	C-II	0.65	0.08	25	
ANR-U2	A-I	0.56	0.12	25	6.59*
	A-II	0.74	0.07	25	
	B-I	0.49	0.10	25	6.90*
	B-II	0.71	0.12	25	
	C-I	0.51	0.14	25	4.96*
	C-II	0.71	0.14	25	
ANR-Ba	A-I	0.65	0.11	25	4.76*
	A-II	0.77	0.07	25	
	B-I	0.55	0.11	25	4.34*
	B-II	0.71	0.15	25	
	C-I	0.54	0.11	25	5.61*
	C-II	0.71	0.10	25	

*$p < .01$.

depth, which were measured on the same line.

In addition, mean adenoidal depth (mean-A) and mean nasopharyngeal depth (mean-N) were separately calculated from 3 adenoidal and nasopharyngeal depths (Table 2). Moreover, the mean of the 3 ANRs was calculated as mean-ANR.

TABLE 4. STATISTICAL ANALYSES OF MEAN-ANR, MEAN-A, AND MEAN-N VALUES OF NORMAL SUBJECTS AND ADENOIDECTOMY CANDIDATES (*T*-TEST)

ANR	*Groups*	*Average*	*SD*	*No.*	t
Mean-ANR	A-I	0.566	0.087	25	7.490*
	A-II	0.729	0.065	25	
	B-I	0.482	0.092	25	6.096*
	B-II	0.676	0.130	25	
	C-I	0.500	0.114	25	6.658*
	C-II	0.690	0.086	25	
Mean-A(cm)	A-I	1.814	0.329	25	3.118*
	A-II	2.135	0.394	25	
	B-I	1.527	0.370	25	5.556*
	B-II	2.117	0.381	25	
	C-I	1.644	0.456	25	5.454*
	C-II	2.242	0.3031	25	
Mean-N(cm)	A-I	3.079	0.405	25	1.013†
	A-II	2.982	0.258	25	
	B-I	3.106	0.326	25	0.641§
	B-II	3.055	0.2268	25	
	C-I	3.232	0.298	25	0.051§
	C-II	3.229	0.2197	25	

*$p < .01$.
†$p < .05$.
§Not significant.

TABLE 5. CORRELATION OF CNOS WITH ADENOIDAL AND NASOPHARYNGEAL PARAMETERS (N = 150)

Parameters	*r*	*p*
Mean-A	.36	<.0001
Mean-N		>.5
Mean-ANR	.68	<.0001
ANR-Sy	.68	<.0001
ANR-U2	.67	<.0001
ANR-Ba	.54	<.0001

Statistical Method. The data were handled with the SPSS statistical package (SPSS for Windows, 5.0.1; 1992). The mean values and standard deviations were calculated as descriptive statistics. In the first instance, the 2 main clinical groups were compared with each other according to age subgroups by using an independent sample *t*-test, and correlations were computed between the CNOS and the variables mean-A, mean-N, mean-ANR, ANR-Sy, ANR-U2, and ANR-Ba. Then, to evaluate the independent effects of age on the variables in each clinical group (controls and PACs), a 1-way ANOVA with Duncan's multiple range test was computed among the 3 age groups within each clinical group (controls and PACs) separately. In addition, the association of age with the variables was checked by correlation analysis within each clinical group (controls and PACs). Last, a 2-way fixed-effects ANOVA was designed to compare the main effects of age and degree of nasal obstruction.

RESULTS

The mean values and standard deviations of all parameters in each subgroup are shown in Tables 3 and 4.

Adenoidal-Nasopharyngeal Ratios. All ANRs and the mean ANR were significantly higher in PACs than in age-matched controls (Tables 3 and 4), and all of them were significantly correlated with the CNOS ($p < .0001$; Table 5). In addition, by 1-way ANOVA, significant decrements in the ANR-Ba, ANR-Sy, and mean-ANR were observed among age groups in control subjects (Table 6) in contrast to PACs (Table 7). Accordingly, the ANR-Ba and mean-ANR had a significantly negative correlation with age in control subjects although none of the ANRs in the PACs had any significant correlation with age (Table 8). When the convenience of the ANRs was tested by a 2-way fixed-effects ANOVA, it was clearly observed that there was no significant difference between controls and PACs in each age group ($p > .5$).

TABLE 6. AGE-ORIENTED DIFFERENCES IN ADENOIDAL AND NASOPHARYNGEAL PARAMETERS IN CONTROL GROUP (1-WAY ANOVA AND DUNCAN TEST; N = 75)

			Groups		
Parameters	*F Ratio*	*p*	*AI-BI*	*AI-CI*	*BI-CI*
Mean-A	3.42	<.05	*	ND	ND
Mean-N	1.56	>.1 (NS)	ND	ND	ND
Mean-ANR	5.05	<.01	*	*	ND
ANR-Sy	4.71	<.02	*	ND	ND
ANR-U2	1.77	>.1 (NS)	ND	ND	ND
ANR-Ba	7.22	<.002	*	*	ND

NS — nonsignificant difference by 1-way ANOVA among 3 groups; * — significant difference with given p level between 2 groups by Duncan test; ND — no difference between 2 groups by Duncan test.

Adenoidal Depth. The mean-A was significantly higher in PACs than in age-matched controls (Table 4). Further, it was significantly correlated with the CNOS in a positive direction (Table 5). On the other hand, the mean-A was found to be significantly decreased in the control group after 71 months by a 1-way ANOVA (Table 6), although no significant decrease by age was observed among PACs (Table 7). By a 2-way fixed-effects ANOVA, no significant difference between controls and PACs in each age group was seen (p > .5).

Nasopharyngeal Depths. No significant difference in the mean-N was observed between the 2 clinical groups (Table 4). Accordingly, correlation analysis disclosed that it was not correlated with the CNOS (Table 5). On the other hand, by a 1-way ANOVA, the mean-N was found to be significantly increased after 95 months of age in PACs (Table 7), whereas no significant difference was observed in control subjects (Table 6). In accordance with these data, a correlation analysis also showed a positive correlation of mean-N with age in PACs in contrast to the control group (Table 8). By a 2-way fixed-effects ANOVA, no significant difference between controls and PACs in each age group was seen (p > .5).

TABLE 7. AGE DIFFERENCES IN ADENOIDAL AND NASOPHARYNGEAL PARAMETERS IN PACs (1-WAY ANOVA AND DUNCAN TEST; N = 75)

			Groups		
Parameters	*F Ratio*	*p*	*AI-BI*	*AI-CI*	*BI-CI*
Mean-A	0.73	>.1 (NS)	ND	ND	ND
Mean-N	5.07	<.01	ND	*	*
Mean-ANR	1.96	>.1 (NS)	ND	ND	ND
ANR-Sy	1.57	>.1 (NS)	ND	ND	ND
ANR-U2	0.64	>.5 (NS)	ND	ND	ND
ANR-Ba	2.47	>.5 (NS)	ND	ND	ND

PACs — possible adenoidectomy candidates, NS — nonsignificant difference by 1-way ANOVA test among 3 groups; * — significant difference with given p level between 2 groups by Duncan test; ND — no difference between 2 groups by Duncan test.

DISCUSSION

In this study, our aim was, first, to find a reliable and practical radiologic parameter for evaluating enlargement of the adenoid. Therefore, we described ANRs different from those described by previous authors.[4,6,7] First, we preferred different landmarks that were easily located on lateral cephalometric radiographs (Fig 2) instead of the original landmark of Fujioka et al[4] on the cranial base (the anteroinferior edge of the sphenobasioccipital synchondrosis), since it was detected with difficulty on radiographs in most patients; these were 2 bony reference points (the posterosuperior edge of sphenobasioccipital synchondrosis and the basion) and 1 adenoidal point (the nearest point of the adenoidal shadow to the posterior nasal spine). Further, we used 1 line to calculate each ANR, in contrast to previous studies.[4,6,7] Thus, the ratio of adenoidal depth to nasopharyngeal depth, which were both measured on the same line (extending from the posterior nasal spine to any of these 3 landmarks, as shown in Table 2 and Fig 1), was calculated as the ANR.

The data in this study clearly demonstrated that each of these ANRs was a reliable objective criterion for evaluation of adenoidal enlargement by physicians. All ANRs presented statistically significant differences between PACs and control groups, and highly significant correlations with clinical symptoms of nasal obstruction. The mean values of our ANRs (0.57, 0.48, and 0.50 for control subjects and 0.73, 0.68, and 0.69 for PACs in age groups of 48 to 71, 72 to 95, and 96 to 120 months, respectively) were similar to previous authors' data,[6,7] although we have used different points that were more practical. Elwany[7] reported that the ANRs of normal children and PACs were 0.58 and 0.71, respectively; Mahboubi et al[6] found the ANRs of 27 adenoidectomy candidates to be 0.71 and 0.69 in the erect and supine positions, respectively. In the study of Fujioka et al,[4] the mean values of symptomatic and asymp-

TABLE 8. CORRELATION OF ADENOIDAL AND NASOPHARYNGEAL PARAMETERS WITH AGE WITHIN EACH CLINICAL GROUP (N = 75 IN EACH CLINICAL GROUP)

	Control Group		PACs	
Parameters	*r*	*p*	*r*	*p*
Mean-A		>.5 (NS)		>.5 (NS)
Mean-N		>.5 (NS)	.36	<.003
Mean-ANR	–.25	<.05		>.5 (NS)
ANR-Sy		>.5 (NS)		>.5 (NS)
ANR-U2		>.1 (NS)		>.5 (NS)
ANR-Ba	–.37	<.002		>.5 (NS)

NS — not significant.

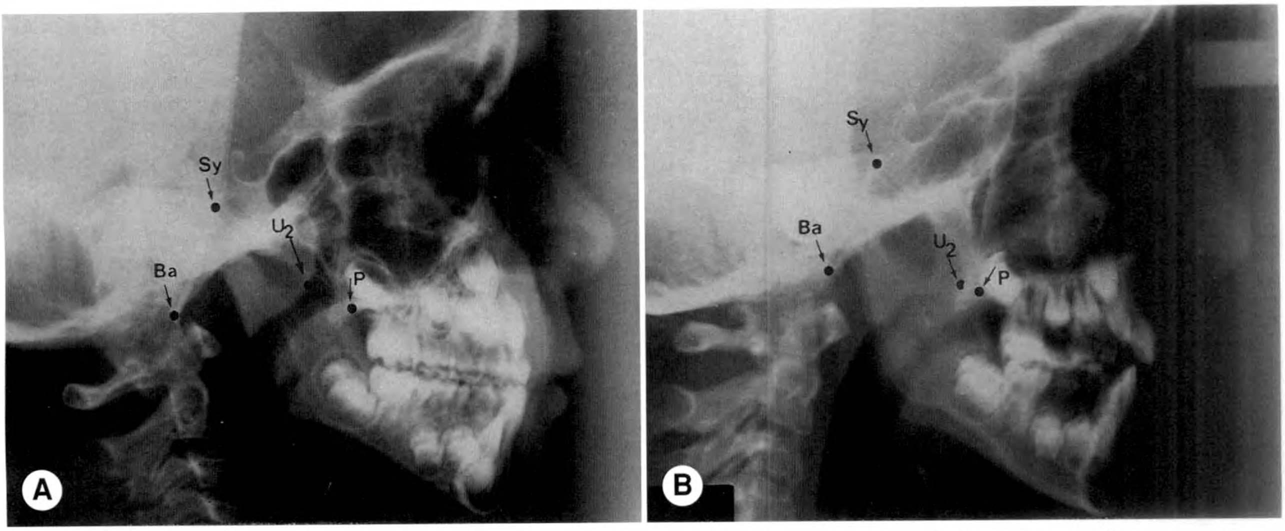


Fig 2. Lateral cephalometric radiographs of A) normal child without any symptoms of nasal obstruction and B) adenoidectomy candidate suffering from mouth breathing, snoring, and sleep apnea. Points (P, Sy, U2, and Ba) used in calculation of ANRs may be easily determined on cephalographs (see Table 2 and Fig 1). Mean ANRs of these cases were about 0.58 and 0.88, respectively.

tomatic children were not clear, because the clinical evaluation of the subjects was not precise enough to yield sufficient data. However, Fujioka et al ascertained that the ANR reached a high value of 0.59 at age 54 months and then gradually decreased to 0.55 at 90 months and 0.51 at 126 months; these values are similar to the mean ANRs of our control groups.

Obstruction of the nasopharynx by the adenoid could be caused by 2 separate processes: an enlarged adenoid or a small nasopharynx, or both. Further, although the mean adenoidal depth decreased with age in normal children, no decrement was observed in PACs. Thus, it could be said that the adenoid is more enlarged, and does not follow a normal regression pattern, in PACs.

Although some researchers believe that nasopharyngeal depth is established early in life, before adenoidal growth is activated, and contributes little to the increase of nasopharyngeal area,[9-11] Linder-Aronson and Woodside[12] reported that the sagittal depth of the nasopharynx increased in both sexes until at least 18 years of age. Moreover, Linder-Aronson[17] pointed out that the sagittal depth was smaller in patients with mouth breathing, and a normalization process was observed after adenoidectomy. Our data showed that the mean nasopharyngeal depth was not smaller in PACs than in normals. Thus, a small nasopharyngeal depth established early in life could not be considered the main reason for nasopharyngeal obstruction due to the adenoid. On the other hand, we did not observe any significant increment in mean nasopharyngeal depth in normal children, in contrast to the data of Linder-Aronson and Woodside.[12] However, the mean nasopharyngeal depth in PACs showed a significant increment after 8 years of age.

Therefore, it could be speculated that a delay in growth activity of the nasopharyngeal depth may play a part in PACs, in addition to abnormalities related to size and the age-dependent regression pattern of adenoidal tissue, which are mainly responsible for nasopharyngeal obstruction due to the adenoid.

This observation also gives support to the assumption that the ANR is a more convenient radiologic parameter for determining whether adenoidal hyperplasia is clinically significant or not, rather than the size of the adenoid or the size of the nasopharynx, because it demonstrates the established state between the size of the nasopharynx and that of the adenoid.

ACKNOWLEDGMENT — The authors thank Sefa Gurcan (research assistant in Department of Biometry, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey) for statistical suggestions.

REFERENCES

1. Hibbert J, Whitehouse GH. The assessment of adenoidal size by radiologic means. Clin Otolaryngol 1978;3:43-7.

2. Johannesson S. Roentgenologic investigation of the nasopharyngeal tonsil in children of different ages. Acta Radiol 1968; 54:299-304.

3. Weitz HL. Roentgenography of adenoids. Radiology 1946; 47:66-70.

4. Fujioka M, Young LW, Girdang BR. Radiographic evaluation of adenoidal size in children: adenoidal-nasopharyngeal ratio. Am J Radiol 1979;133:401-4.

5. Linder-Aronson S. Adenoids: their effect on mode of breathing and nasal airflow and their relationship to character-

istics of the facial skeleton and the dentition. Acta Otolaryngol [Suppl] (Stockh) 1970(suppl 265).

6. Mahboubi S, Marsh RR, Potsic WP, Pasquariello PS. The lateral neck radiograph in adenotonsillar hyperplasia. Int J Pediatr Otorhinolaryngol 1985;10:67-73.

7. Elwany S. The adenoidal-nasopharyngeal ratio (AN ratio): its validity in selecting children for adenoidectomy. J Laryngol Otol 1987;101:569-73.

8. Goksu N, Kemaloglu YK, Akyildiz N, Bayramoglu I. Adenoidal-nasopharyngeal ratio: an objective parameter in selecting children for adenoidectomy. Gazi Med J 1990;1:183-8.

9. Brodie AG. On the growth pattern of the human head from the third month to the eighth year of life. Am J Anat 1941; 68:209-62.

10. King EW. A roentgenographic study of pharyngeal growth. Angle Orthod 1952;22:23-37.

11. Handelman CS, Osborne G. Growth of nasopharynx and adenoid development from one to eighteen years. Angle Orthod 1976;46:243-59.

12. Linder-Aronson S, Woodside DG. The growth in sagittal depth of the bony nasopharynx in relation to some other facial variables. In: McNamara JA Jr, ed. Naso-respiratory function and craniofacial growth. Ann Arbor, Mich: University of Michigan, 1979:27-40.

13. Subtelny JD. Oral respiration: facial maldevelopment and corrective dentofacial orthopedics. Angle Orthod 1980;50:147-64.

14. Jeans WD, Fernando DCJ, Maw AR, Leighton BC. A longitudinal study of the growth of the nasopharynx and its contents in normal children. Br J Radiol 1981;54:117-21.

15. Latham RA. The sella point and postnasal growth of the human cranial base. Am J Orthod 1972;61:156-62.

16. Rickets RM. The cranial base and soft structures in cleft palate speech and breathing. Plast Reconstr Surg 1954;14:647-61.

17. Linder-Aronson S. Naso-respiratory function and craniofacial growth. In: McNamara JA Jr, ed. Naso-respiratory function and craniofacial growth. Ann Arbor, Mich: University of Michigan, 1979:121-48.

≈

RHINOLOGY SYMPOSIA

The 18th International Symposium on Infection and Allergy of the Nose (ISIAN), the 4th Asian Research Symposium on Rhinology (ARSR), and the 3rd ASEAN Rhinology Group Congress (ARC) will be held in Manila, Philippines, February 14-18, 1999. For information, contact Gil M. Vicente, MD, Congress President, Dept of ORL-HNS, Jose Reyes Memorial Medical Center, Rizal Avenue Sta. Cruz, Manila, Philippines 1003; telephone (632) 743-6921; fax (632) 732-1077 or (632) 522-0946; e-mail isian@psohns.com; web site http://www.psohns.com/isian.

Ann Otol Rhinol Laryngol 108:1999

CHANGES IN HEAD AND NECK TUMOR HYPOXIC FRACTION DURING SPLIT-COURSE RADIOCHEMOTHERAPY

RAINER JUND, MD
HORST-JÜRGEN FELDMANN, MD
PETER STADLER, MD
BARBARA WOLLENBERG, MD
MICHAEL MOLLS, PHD
MUNICH, GERMANY

This study explored patterns of oxygen distribution in human tumors during primary radiochemotherapy. Patients with positive nodes from head and neck squamous cell carcinoma ($n = 15$) were investigated before therapy, before and after a 2-week respite, and at the end of the treatment. Intratumoral tissue oxygen tension (pO2) was measured with sterile polarographic needle electrodes and a computerized histography system. The 2 lowest pO2 classes, ie, 0 and 5 mm Hg, were designated the hypoxic fraction, and the mean and median pO2 were evaluated for each tumor. In the beginning, a marked variability in tissue pO2 was found. The initial size of the hypoxic fraction ranged from 0% to 61% of measured values. At the end of treatment, 4 tumors showed an increase in mean pO2, and 7 tumors a lower mean pO2 in comparison to the initial values. However, an impressive finding was that the hypoxic fraction of 9 tumors became smaller during the pause, 1 tumor showed no change, and 1 showed an increase in hypoxic fraction. The results show that there is a widely distributed tissue oxygenation with marked hypoxic zones in human neck nodes. During radiochemotherapy, tissue oxygenation changed, with great intertumor variability. A tendency toward a decrease of the hypoxic fraction after the respite could be seen. This change in tumor oxygenation during therapy needs further evaluation.

KEY WORDS — neck nodes, radiochemotherapy, tumor oxygenation, tumor physiology.

INTRODUCTION

It is well known that hypoxic cells are present in rodent and xenografted human tumors.[1,2] Hypoxia is regarded to be an important factor in radioresistance, as 2 to 3 times higher radiation doses are needed to kill hypoxic cells when compared with well-oxygenated cells.[3,4] Therefore, the presence of hypoxic clonogenic cells could be a major factor influencing the response of tumors to radiotherapy and cytotoxic drugs.[5-7]

During fractionated radiotherapy, it should be interesting to evaluate changes of the oxygenation status of the patients. At present, it is not clear if there exists any kind of reoxygenation under radiotherapy. Up to now, little has been published on follow-up of intratumoral tissue oxygen tension (pO2) during radiotherapy or radiochemotherapy of human tumors.[8] Therefore, we have been measuring the oxygenation status in human head and neck tumors before, during, and after radiochemotherapy to investigate the course of pO2 distribution, especially of the hypoxic fraction.

MATERIAL AND METHODS

Patients. A total of 15 patients with neck nodes from primary head and neck tumors were investigated pretherapeutically and during radiotherapy and radiochemotherapy. Each patient signed a written consent form approved by the University of Munich Board for Human Subject Studies. Patient and tumor characteristics are shown in Table 1. The tumors were classified according to the TNM staging system (AJC-UICC 1993).

Data for volume calculation were determined with ultrasound, computed tomography (CT), or magnetic resonance imaging. Three diameters (a, b, and c) of the nodes or the primary were measured, and the approximate volumes were calculated with a simplified algorithm ($\text{volume} = 0.5 \times a \times b \times c$). Remission rates were classified according to measurable reduction in tumor volumes 9 months after the end of therapy: 1) total remission, when no tumor could be clinically detected, 2) partial remission, when reduction in tumor volumes was about 50% as estimated on CT imaging, 3) no change, or 4) progressive disease. All patients underwent primary radiochemotherapy. The usual schedule was a split-course treatment with a 2-week pause after 30 Gy. The final dose to the tumor consisted of 70 Gy. The fractionation was 2 Gy every day. In weeks 1 and 3, the patients received simultaneous chemotherapy: 15 mg/m^2 mitomycin C on day 1 of the course as a bolus injection and 750 mg/m^2 5-fluorouracil on days 1 through 5 of the course

---

From the Department of Otorhinolaryngology–Head and Neck Surgery, University of Munich, Klinikum Grosshadern (Jund, Wollenberg), and the Department of Radiooncology, Technical University Munich (Feldmann, Stadler, Molls), Munich, Germany.

CORRESPONDENCE — Rainer Jund, MD, Dept of Otorhinolaryngology–Head and Neck Surgery, University of Munich, Klinikum Grosshadern, Marchioninistr 15, 81377 München, Germany.

TABLE 1. PATIENTS INCLUDED IN STUDY AND TUMOR DATA

Patient No.	*Sex*	*Age*	*Primary*	*TNM*	*Volume (cm^3)*	*Measured Area*
1	M	55	Hypopharynx	T4N2bM0G2	75	Neck node
2	F	77	Oropharynx	T2N2aM0G2	12	Neck node
3	M	53	Hypopharynx	T3N2bM0G2	9	Neck node
4	F	92	Oropharynx	T2N2bM0G2	9	Neck node
5	F	62	Floor of mouth	T4N2aM0G3	50	Primary
6	M	47	Floor of mouth	T4N2cM0G2	37	Primary
7	M	57	Oropharynx	T4N2bM0G2	50	Neck node
8	M	43	Oropharynx	T4N2cM0G2	12	Neck node
9	M	40	Hypopharynx	T4N2bM0G3	30	Neck node
10	M	55	Floor of mouth	T4N2aM0G2	62	Primary
11	F	74	Oropharynx	T4N3M0G2	24	Neck node
12	M	54	Anterior or lateral tongue	T4N2bM0G3	6	Primary
13	M	45	Anterior or lateral tongue	T4N2cM0G2	63	Primary
14	M	56	Oropharynx	T3N2bM0G3	8	Neck node
15	M	49	Hypopharynx	T4N3M0G3	18	Neck node

as a continuous infusion.

Measurement of Tissue Oxygenation. The series of pO2 measurements in all cases consisted of an initial investigation, an investigation after 30 Gy before a pause, after the pause, and at the end of the therapy, usually after 70 Gy and 2 courses of concomitant chemotherapy. Figure 1 shows the treatment schedule and the time points of measurements.

Intratumoral pO2 measurements were performed with sterile polarographic needle electrodes and the Eppendorf computerized histography system (Fleckenstein; Eppendorf, Hamburg, Germany). The outer tips of the probes had a diameter of 200 to 300 µm. Detailed technical data of the needle electrodes, the calibration procedure, and the data display have been described.[9,10] After local anesthesia (Scandicain 1%, Astra Chemicals), a plastic trocar (0.8 mm outer diameter) with a hypodermic needle was inserted into the tumor periphery. The insertion was defined clinically and by ultrasound. The insertion point was marked with a water-resistant pen, and the direction of the tracks was documented by ultrasound. The hypodermic needle was then removed and the oxygen sensor was placed into the tissue. In all tumors, 3 radial tracks were evaluated, guided in 3 different directions (1 median and 2 eccentric tracks).[11] The tumor was penetrated in forward steps of at most 1.0 mm. After a rapid backward motion (0.3 mm) was made in order to minimize compression effects, the signal of the probe was registered 1.4 seconds after the backward motion. Up to 200 tumor points and at least 120 were measured within a short period of time. The data were obtained as pO2 histograms with a class width of 2.5 mm Hg. The 2 lowest pO2 classes, ie, 0 and 5 mm Hg, were designated as the hypoxic fraction, and the mean and median pO2 were evaluated for each tumor. As control measurements, in some patients subcutaneous tissue and normal oral mucosa were measured. Calibration was done before and after the measurements (oxygen drift) with a sterile phosphate-buffered saline solution (pH 8) equilibrated with air or 100% nitrogen (gas bubbling) at room temperature. The values were corrected for the barometric pressure and the temperature of the tissue. A complete procedure was limited to 20 minutes to ensure good patient compliance.

To exclude the influence of systemic parameters and factors related to the arterial oxygen concentration, we recorded heart rate, blood pressure, hemoglobin concentration, and arterial blood gases for each patient at the time point of measurement.

RESULTS

The invasive procedure was tolerated without any pain by most of the patients, even at the end of treatment.

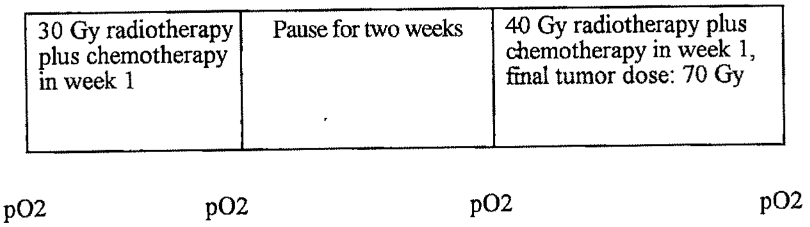

30 Gy radiotherapy plus chemotherapy in week 1
Pause for two weeks
40 Gy radiotherapy plus chemotherapy in week 1, final tumor dose: 70 Gy
pO2
pO2
pO2
pO2

Fig 1. Schematic of radiochemotherapy and time points of intratumoral tissue oxygen tension (pO2) measurements.

TABLE 2. MEAN AND MEDIAN INTRATUMORAL TISSUE OXYGEN TENSION

Patient No.	*Initial*	*Before Pause*	*After Pause*	*End of Treatment*
1	46.6 (42)	31.3 (32)	35.1 (36)	17.6 (6)
2	2.4 (8)	42.2 (49)	25.3 (28)	
3	46.3 (46)	40.6 (35)	6.3 (6)	23.0 (21)
4	25.8 (24)	6.9 (8)	51.2 (55)	23.8 (25)
5	12.8 (18)	23.2 (23)	37.9 (38)	22.5 (29)
6	8.3 (10)	12.2 (15)	12.0 (10)	7.9 (9)
7	43.0 (40)	21.2 (23)		
8	20.9 (17)	18.0 (19)	40.4 (44)	28.0 (28)
9	16.9 (19)	18.0 (16)	40.1 (46)	
10	21.9 (23)	17.0 (16)	20.0 (18)	26.0 (23)
11	8.0 (2)	1.5 (3)		
12	5.2 (3)		18.0 (19)	11.7 (14)
13	35.6 (37)			4.8 (6)
14	26.5 (24)	20.0 (24)	17.2 (19)	14.0 (17)
15	31.4 (28)	12.6 (9)	28.3 (29)	8.4 (9)

Data are in millimeters of mercury. Median values are in parentheses.

In 3 patients it was not possible to complete the series, because the node became too small for the measurement technique (no tumor); in 1 patient the tumor region developed a necrotic consistency that allowed no puncture (patient 11). One of the patients died of cardiopulmonary disease a short time after the second measurement. The mean and median values of all patients for every time point are shown in Table 2.

We made the general observation that within the same tumor site and within tumors with the same TNM and histopathologic staging the distribution of pO2 revealed a remarkable variability and ranged in mean pO2 from 46.6 to 2.4 mm Hg (Table 2). The same was observed for the course of the median pO2 (Table 2). The initial hypoxic fraction of the tumors ranged between 0% and 61% (Table 3). No correlation with tumor size, TNM staging, or histopathologic grading was found. We detected no difference in age, sex, or origin of the primary between the cases with a low hypoxic fraction and those with a higher one. The systemic parameters of the patients, eg, blood pressure and hemoglobin, were within normal ranges, and therefore no correlation to our oxygenation data is displayed. In Fig 2, the course of the median pO2 values during therapy is shown. Figure 3 demonstrates the course of the hypoxic fraction

TABLE 3. HYPOXIC FRACTION (IN PERCENT) OF OXYGEN DISTRIBUTION IN TUMORS

Patient No.	*Initial*	*Before Pause*	*After Pause*	*End*
1	0.0	17.3	11.3	44.0
2	41.3	0.0	0.0	
3	4.0	0.0	33.0	31.0
4	22.6	32.0	0.0	36.0
5	39.0	24.0	3.3	36.0
6	48.0	39.3	22.0	32.0
7	0.0	4.6		
8	28.0	29.0	4.0	30.0
9	18.6	28.0	8.0	
10	3.3	40.0	28.5	33.0
11	61.3	80.0		
12	46.0		20.0	29.0
13	29.5			63.0
14	10.0	47.5	27.6	39.0
15	27.3	54.3	11.2	51.8

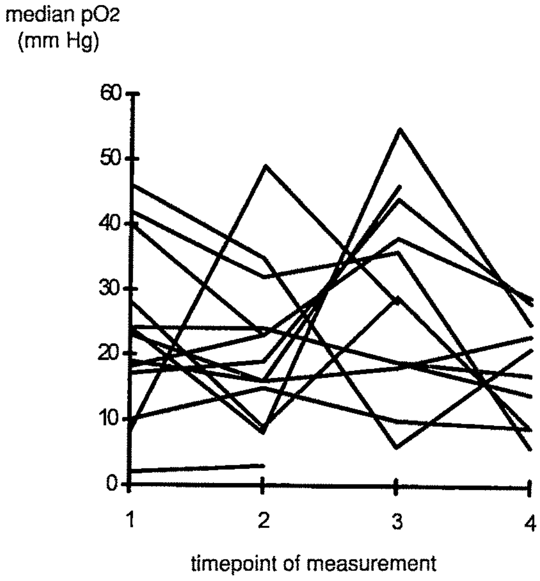


Fig 2. Course of median pO2 during therapy for each patient.

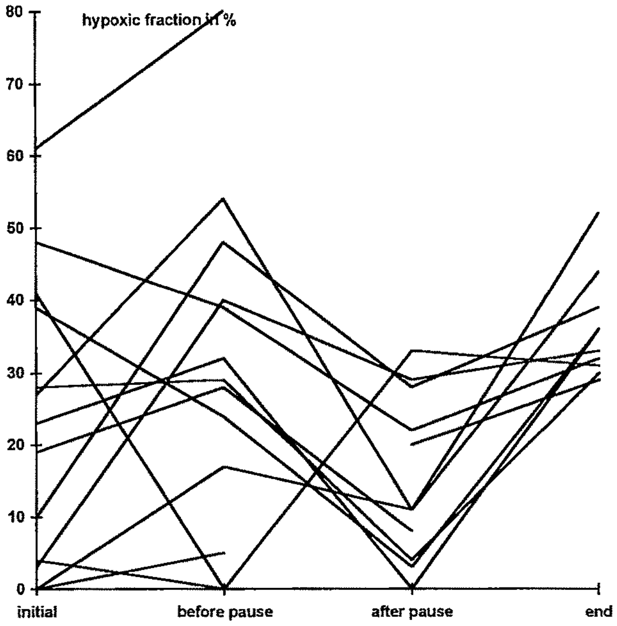


Fig 3. Course of hypoxic fraction during therapy for each patient.

TABLE 4. INITIAL HYPOXIC FRACTION, INITIAL MEAN INTRATUMORAL TISSUE OXYGEN TENSION, AND INITIAL RESPONSE TO THERAPY AFTER NINE MONTHS

Patient No.	*Hypoxic Fraction (%)*	*Mean pO2 (mm Hg)*	*Initial Response After 9 Months*
1	0.0	46.6	CR
2	41.3	2.4	CR
3	4.0	46.3	CR
4	22.6	25.8	PR
5	39.0	12.8	PR
6	48.0	8.3	PR
7	0.0	43.0	
8	28.0	20.9	PR
9	18.6	16.9	CR
10	3.3	21.9	PR
11	61.3	8.0	PR
12	46.0	5.2	CR
13	29.5	35.6	PR
14	10.0	26.5	CR
15	27.3	31.4	PR

CR — complete response, PR — partial response. Patient 7 died of cardiopulmonary disease.

during therapy.

After a 14-day-long respite, in 9 tumors the size of the hypoxic fraction became less extensive, in 1 tumor the hypoxic fraction was larger, and in 1 case there was no change (Fig 3). At the end of the therapy, the hypoxic fraction changed, in 7 cases toward a larger one and in 3 tumors to a smaller one.

No correlation between the initial hypoxic fraction, pO2, and the values at the end of the therapy within the individual cases was found.

So far, the data also indicate that there was no correlation between the initial tumor oxygenation, the size of the hypoxic fraction, and the initial tumor response (Table 4).

DISCUSSION

Because of the potential role of tumor oxygenation in radiotherapy and also in chemotherapy, interest in measurement of human tumor oxygen levels has existed since the 1950s, when significant hypoxia in human tumor was demonstrated by polarographic techniques.[12] The technical limitations of the equipment used, eg, compression effects and a large needle diameter, made the results of these studies sometimes difficult to interpret.[12,13] These limitations have been overcome by using the Eppendorf computerized histograph, which causes minimal pathologic modification of the evaluated tissue.[14] No adverse effects of this technique on the natural history of tumors in mice, regarding the tumor growth and the number of lung metastases, could be found.[15] Some studies have strongly suggested a correlation between direct pO2 measurements and radiobiological tumor hypoxia.[16] However, another study found no such relationship.[17]

In control measurements of normal tissue of the skin and oral mucosa in some of the patients, we repeatedly found a mean pO2 of 55 and 51 mm Hg, respectively (data not shown). This is in good accordance with the literature for normal tissue oxygenation, as evaluated with this technique.[18] The results of our study indicate that oxygen levels lower than those of surrounding normal tissue are uniformly present in human head and neck tumors. A relatively broad hypoxic fraction is common. These data are in accordance with the marked hypoxia in several human tumors identified with this method, including cervix carcinomas,[19] breast carcinomas,[10,20] recurrent soft tissue sarcomas, and rectal cancers.[11] It was also shown that human head and neck tumors have areas with low levels of pO2.[21,22] In our study, most tumors had a relatively large percentage of pO2 values below 5 mm Hg, defined as the hypoxic fraction. The hypoxic fraction could be a useful indicator of the presence of hypoxia. At this pO2 level, a clinically significant low radiosensitivity due to hypoxia can be expected. Therefore, it should be interesting to see whether the size of the hypoxic fraction does change during radiochemotherapy. This could reflect, together with clinical data, the course of hypoxia within the tumor during therapy. Our data show that hypoxic fractions change their extent within the tumor during therapy. Within the same tumor, no correlation between initial and end point hypoxic fractions could be seen. One might expect that a large hypoxic fraction at the beginning of the therapy means a large therapy-resistant portion of the tumor, which may be expressed in an ongoing large hypoxic fraction at the end. We think the irregular changes are due to possible differences in tumor biology, especially in vascularization and its changes during therapy. As the vascular supply of the tumor is diminished, it is likely that tumor cells progress from oxygenated to anoxic and necrotic conditions. In many cases at the end of the therapy, hypoxia increased and mean pO2 decreased. This could be due to radiation-induced necrosis of the tumor and replacement with fibrosis. With the reacquisition of a state of cellular oxygenation by the formerly hypoxic survivors of a given radiation exposure, a reacquisition of radiosensitivity should be associated. This phenomenon, reoxygenation, is observed under laboratory conditions in cell lines and murine tumor models.[23,24] A proposed mechanism, that the shrinkage undergone by a tumor during the course of treatment causes reoxygenation by bringing the blood supply closer to the relevant cells, may contribute to the process.[25]

However, we observed a tendency toward an increased oxygenation after the pause, but at the end of the treatment our measurements showed an increase in tumor hypoxia (Figs 2 and 3). The time course of changes in oxygenation known from previous studies ranged from hours, in a transplanted mouse mammary carcinoma,[26] to a few days, in a transplanted mouse osteosarcoma.[27] All these studies present data from animal models, which grow relatively rapidly, and the intratumoral mechanisms that take place in human tumors in vivo and are possibly capable of improving tumor oxygenation could need more time. Our data show no correlation between the initial size of the hypoxic fraction, the mean pO2, and the response to therapy. However, the number of studied cases is too low for us to perform a statistically significant analysis. Our cases are selected cases in the sense of the expected compliance of the patients and the good physical performance. Maybe this is one reason for the relatively good treatment outcome. Another advantage is possibly the addition of chemotherapy. However, the time of posttreatment control is yet too short to report on disease-free intervals.

In conclusion, the measurement of pO2 distribution in human tumors could be helpful in developing strategies to improve therapy. Much more information is needed to help us arrive at a comprehensive understanding of the true significance of human tumor oxygenation for treatment.

REFERENCES

1. Chapman JD. The detection and measurement of hypoxic cells in solid tumors. Cancer 1984;54:2441-9.

2. Moulder JE, Rockwell S. Hypoxic fractions of solid tumors: experimental techniques, methods of analysis and a survey of existing data. Int J Radiat Oncol Biol Phys 1984;10:695-712.

3. Evans NTS, Naylor PFD. The effect of oxygen breathing and radiotherapy upon the tissue oxygen tension of some human tumors. Br J Radiol 1963;36:418-25.

4. Gray LH, Conger AD, Ebert M, Hornsey S, Scott OCA. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol 1953;26:638-48.

5. Overgaard J. Sensitization of hypoxic tumor cells. Clinical experience. Int J Radiat Biol 1989;56:801-11.

6. Sakata K, Tak Kwok T, Murphy BJ, Laderoute KR, Gordon GR, Sutherland RM. Hypoxia-induced drug resistance: comparison to P-glycoprotein–associated drug resistance. Br J Cancer 1991;64:809-14.

7. Bush RS, Jenkin RDT, Allt WEC, Beale FA, Bean H, Dembo AJ. Definitive evidence for hypoxic cells influencing cure in cancer therapy. Br J Cancer Suppl 1978;37(suppl 3):302-6.

8. Jund R, Feldmann HJ, Molls M. Der Sauerstoffpartialdruck im Gewebe menschlicher Kopf-Hals-Karzinome während primärer Radio-Chemotherapie. Laryngorhinootologie 1996;75:43-7.

9. Höckel M, Schlenger K, Knoop C, Vaupel P. Oxygenation of carcinomas of the uterine cervix: evaluation by computerized O2 tension measurements. Cancer Res 1991;51:6098-102.

10. Vaupel P, Schlenger K, Knoop C, Höckel M. Oxygenation of human tumors: evaluation of tissue oxygen distribution in breast cancers by computerized O2 tension measurements. Cancer Res 1991;51:3316-22.

11. Feldmann HJ, Molls M, Auberger T, Stüben G. Oxygenation and perfusion status of recurrent human tumors. In: Vaupel P, ed. Tumor oxygenation. Stuttgart, Germany: Gustav Fischer Verlag, 1994:319-26.

12. Cater DB, Silver IA. Quantitative measurements of oxygen tension in normal tissue and in the tumors of patients before and after radiotherapy. Acta Radiol 1960;53:233-56.

13. Kolstad P. Intercapillary distance, oxygen tension and local recurrence in cervix cancer. Scand J Clin Lab Invest Suppl 1968;106(suppl):145-57.

14. Schramm U, Fleckenstein W, Weber C. Morphological assessment of skeletal muscular injury caused by pO2 measurements with hypodermic needle probes. In: Ehrly AM, Fleckenstein W, Hauss J, Juch R, eds. Clinical oxygen pressure measurement II. Berlin, Germany: Blackwell Ueberreuter Wissenschaft, 1990:38-50.

15. Lartigau E, Lespinasse F, Vitu L, Guichard M. Does the direct measurement of oxygen tension in tumors have any adverse effects? Int J Radiat Oncol Biol Phys 1991;22:949-51.

16. Horsman MR, Khalil AA, Siemann DW, et al. Relationship between radiobiological hypoxia in tumors and electrode measurements of tumor oxygenation. Int J Radiat Oncol Biol Phys 1994;29:439-42.

17. Fenton BM, Kiani MF, Siemann DW. Should direct measurements of tumor oxygenation relate to the radiobiological hypoxic fraction of a tumor? Int J Radiat Oncol Biol Phys 1995; 33:365-73.

18. Saumweber DM, Kau RJ, Arnold W. Tumor tissue oxygenation in primary squamous cell carcinomas of the head and neck. Preliminary results. In: Vaupel P, Kelleher DK, Günderoth M, eds. Tumor oxygenation. Stuttgart, Germany: Fischer, 1995: 313-7.

19. Höckel M, Knoop C, Schlenger K, et al. Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Radiother Oncol 1993;26:45-50.

20. Füller J, Feldmann HJ, Molls M, Sack H. Untersuchungen zum Sauerstoffpartialdruck im Tumorgewebe unter Radiound Thermoradiotherapie. Strahlenther Onkol 1994;170:453-60.

21. Gatenby RA, Kessler HB, Rosenblum JS, Coia LR, Moldofsky PJ, Hartz WH. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radi-

ation therapy. Int J Radiat Oncol Biol Phys 1988;14:831-8.

22. Lartigau E, Le Ridant AM, Lambin P, et al. Oxygenation of head and neck tumors. Cancer 1993;71:2319-25.

23. Kallman RF, Jardine LJ, Johnson CW. Effects of different schedules of dose fractionation on the oxygenation status of a transplantable mouse sarcoma. J Natl Cancer Inst 1970;44:369-77.

24. Van Putten LM, Kallmann RF. Oxygenation status of a transplantable tumor during fractionated radiation therapy. J Natl Cancer Inst 1968;40:441-51.

25. Kallman RF. The phenomenon of reoxygenation and its implications for fractionated radiotherapy. Radiology 1968;105: 135-42.

26. Howes AE. An estimation of changes in the proportions and absolute numbers of hypoxic cells after irradiation of transplanted C3H mouse mammary tumors. Br J Radiol 1969;42:441-7.

27. Van Putten LM. Tumour reoxygenation during fractionated radiotherapy; studies with a transplantable mouse osteosarcoma. Eur J Cancer 1978;4:173-82.

≈

ADVANCED EAR SURGERY

A Compact Training Course in Advanced Ear Surgery (Endaural Tympano-meatoplasty and Enlarged Middle Fossa Approach) will be held May 16-19, 1999, in Erlangen-Nuremberg, Germany. For information, contact Prof Dr M. E. Wigand, Dept of ORL, University of Erlangen-Nuremberg, HNO Universitatsklinik, Waldstrasse 1, D-91054, Erlangen, Germany; telephone +49/9131/85-3141; fax +49/9131/85-6857.

Ann Otol Rhinol Laryngol 108:1999

TITANIUM VOCAL FOLD MEDIALIZING IMPLANT: INTRODUCING A NOVEL IMPLANT SYSTEM FOR EXTERNAL VOCAL FOLD MEDIALIZATION

GERHARD FRIEDRICH, MD
GRAZ, AUSTRIA

With the increasing worldwide spread of the Isshiki technique for external vocal fold medialization, some disadvantages and limitations have also emerged, and an increasing demand for a ready-made and standardized implant system can be observed. For this reason, I started experimental and clinical investigations with the goal of replacing the silicone with a safer material, and also simplifying and standardizing the surgical procedure. In particular, the danger of implant dislocation should be excluded with greater certainty. As a result, I have developed an implant made of medical-grade titanium. My surgical experiences in 20 patients with this newly developed titanium vocal fold medializing implant revealed that vocal fold medialization could be performed easily and that no perioperative complications occurred in any case. The major advantage was a significant reduction of operative time due to the preformed implant. This is not only more convenient for both the surgeon and the patient, but is also critical for obtaining optimal results due to the reduced intralaryngeal swelling and hematoma. The reduction of the glottic gap by the operation was statistically significant. Significant improvement of all voice parameters was achieved and demonstrated by a statistically significant reduction of the voice dysfunction index. Compared to the current techniques and implant systems, I see the following additional advantages: 1) titanium is a relatively safe implant material with excellent biocompatibility; 2) the design of the implant ensures optimal fixation and stabilization; 3) the implantation technique and handling is simple and time-saving; 4) the titanium sheet is easy to shape and adapt to the individual situation; and 5) only 2 sizes of implants, and no expensive instruments, are required.

KEY WORDS — glottic insufficiency, laryngeal framework surgery, laryngoplasty, phonosurgery, thyroplasty, titanium implant, unilateral laryngeal palsy, vocal fold medialization.

INTRODUCTION

When Isshiki et al,[1,2] in the 1970s, took up Payr's[3] idea of external vocal fold medialization and modified and systematized it as thyroplasty type I, this technique gained widespread acceptance as a standard procedure for the treatment of glottic insufficiencies, particularly in unilateral vocal fold palsyses. In accordance with numerous reports in the literature, my own results with this technique have been rather satisfactory.[1,2,4-14] Nevertheless, similar to other authors, I experienced some disadvantages and limitations of the "Isshiki method," concerning both the implant and the surgical technique[4,7,12,13] (Table 1).

Despite only 1 report[15] of an allergic reaction to a silicone implant in thyroplasty, concerns about silicone as permanent implant material are increasing.[16,17] Therefore, several researchers have developed implants made of alternative materials, such as Vitallium (miniplates),[17] ceramic,[18] Gore-Tex,[19] and hydroxylapatite.[4]

TABLE 1. DISADVANTAGES OF ISSHIKI TECHNIQUE

- Implant
  - Silicone is used as implant material.
  - Manufacturing is time-consuming and not standardized.
  - Fixation is difficult, with potential of dislocation.
- Technique
  - Mobilization of cartilage window is not always atraumatic.
  - Cartilage is not ideal for support, and can dislocate, be resorbed, and/or form regenerates.
  - Intact perichondrium can hinder sufficient medialization.

On-site freehand carving of the implant is time-consuming, prolonging the operation time and causing a vast number of different modifications in the sizes and shapes of implants being used. This can be especially a problem for the beginner and may result in suboptimal shaping, and hinders the spread of this technique.[4,5,9,13,14,20]

Since silicone rubber does not connect to the surrounding tissues, the implant stability is poor, leading to insufficient silicone block fixation.[16,21] Although not experienced in my own cases, dislocation of silicone implants have been reported several times and can cause a dangerous situation if the implant enters the airway.[4,9,10,22-24]

The technique of cutting and mobilizing the cartilage window is often not as atraumatic as required. A lesion of the inner perichondrium cannot be avoided in every case, and bleeding is difficult to control through the small incision. Increased swelling and

---

From the ENT-University Hospital, University Medical School Graz, Graz, Austria.

CORRESPONDENCE — Gerhard Friedrich, MD, ENT-University Hospital, University Medical School Graz, Auenbruggerplatz 20, A-8036 Graz, Austria.

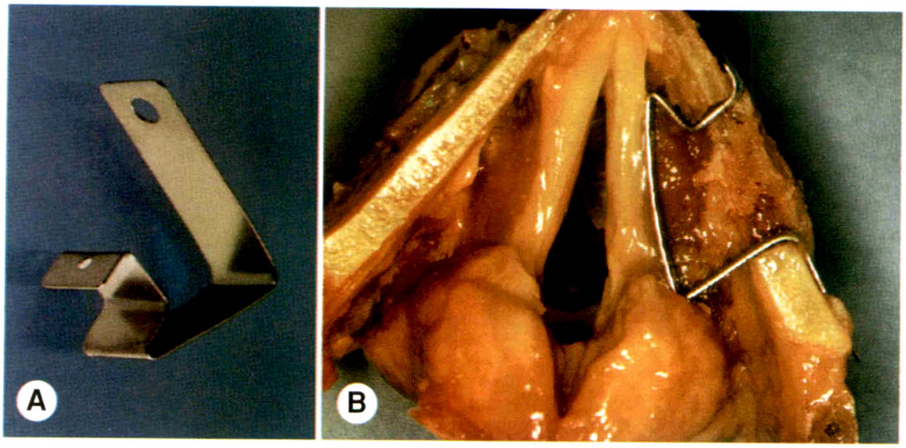


Fig 1. Titanium vocal fold medializing implant (TVFMI). A) Alone. B) Inserted in specimen.

edema of the endolaryngeal tissue may result, making it difficult to estimate the amount of optimal medialization.[20]

The cartilage island used for the medialization can dislocate, be resorbed in an uncertain amount, and/or form regenerates. Moreover, it is not an ideal support for the vocal fold, because of its natural shape, which can result in an overadduction of the anterior portion of the vocal fold.[5,14,25]

Preservation of the inner perichondrium can hinder sufficient medialization, leading to underadduction and, consequently, poor outcome.[12,14]

For these reasons, I started experimental and clinical investigations with the goal of replacing silicone with a safer material, and simplifying and standardizing the surgical procedure. In particular, the danger of implant dislocation should be excluded with great certainty. In collaboration with the Heinz Kurz Company, Dusslingen, Germany, I have developed an implant made of medical-grade titanium (Fig 1). The first clinical results obtained with this titanium vocal fold medializing implant (TVFMI) will be reported.

MATERIAL AND METHODS

After approval by the Ethics Committee of the Medical Faculty of the University of Graz, I performed an external vocal fold medialization using the TVFMI in 20 patients from July 1996 to September 1997. All operations were performed by the author. Descriptive data are shown in Table 2. The indication for operation was glottic insufficiency that could not be successfully treated by voice therapy. With the exception of 2 cases (Nos. 3 and 8), the underlying cause was a unilateral laryngeal palsy. Usually, I perform the operation no earlier than 6 months after onset, unless malignant disease is involved (eg, lung carcinoma).[7]

Preoperatively and postoperatively (2, 6, and 12 months), the patients were comprehensively evaluated. The grade of glottic insufficiency was evaluated by videolaryngoscopy and videostroboscopy (Kay Elemetrics stroboscope, 70° rigid laryngoscope) on a standardized scale from 0 (complete glottic closure, paralyzed vocal fold in medial position) to 3 (extreme insufficient glottic closure, paralyzed vocal fold in lateral position)[5,7] (Table 2).

Voice function testing was done by measuring the mean fundamental frequency and sound pressure level; the singing, speaking, and shouting voice range profile (Phonomat, Homoth); and aerodynamic parameters, in particular, maximum phonation time. Voice sound was assessed on a roughness, breathiness, hoarseness (RBH) scale from 0 (no disturbance) to 3 (extreme hoarseness).[26] Electroacoustic voice analysis was done by means of the Computerized Speech Lab (CSL) with the Multi-Dimensional Voice Program (MDVP, Kay Elemetrics).[27] The impairment of vocal communication skills according to the individual, professional, and social situation of the patient was rated on a newly developed scale (0 being no voice impairment even in professional voice use; 1 being no voice impairment in the needs of everyday communication, with slight limitations in voice capacity; 2 being slight voice impairment in the needs of everyday communication, with marked limitations in voice capacity; and 3 being a voice capacity that is extremely limited, with problems even in everyday communication).[7,8,26] For global assessment of vocal abilities, a combination parameter called the voice dysfunction index was calculated from the grade of hoarseness, impairment of vocal communication skills, maximum phonation time, intensity, and frequency range[8] (Table 2). The conditions, requirements, performance measurements, normative data, and cutoff scores have been previously described in detail.[8,26]

Statistical analysis was performed with the computer statistical program SPSS for Windows 7.5 2G and

TABLE 2. DESCRIPTIVE AND STATISTICAL DATA

Pt No.	*Age*	*Sex*	*Side*	*Date of Operation*	*Size of Implant (mm)*	*Diagnosis*	*Glottal Gap*			*Voice Dysfunction Index*		
							Preop	*Difference*	*Postop*	*Preop*	*Difference*	*Postop*
1	41	F	R	July 12, 1996	13	Thyroidectomy	1.0	0.5	0.5	1.6	1.1	0.5
2	74	F	L	Oct 14, 1996	13	Thyroidectomy	2.5	2.0	0.5	2.0	0.9	1.1
3	49	F	L	Oct 21, 1996	15	Vocal fold scar	1.0	1.0	0.0	1.0	0.2	0.8
4	83	F	R	Nov 5, 1996	13	Thyroidectomy	1.5	1.0	0.5	1.2	0.4	0.8
5	65	M	L	Nov 20, 1996	13	Idiopathic palsy	2.0	1.0	1.0	2.0	1.0	1.0
6	76	F	L	Nov 25, 1996	13	Idiopathic palsy	3.0	1.5	1.5	2.6	1.5	1.1
7	51	F	L	Nov 26, 1996	15	Thyroidectomy	1.5	1.5	0.0	1.4	0.6	0.8
8	43	M	R	Dec 11, 1996	15	Cordectomy	3.0	1.0	2.0	3.0	1.4	1.6
9	50	M	L	Jan 10, 1997	15	Lung carcinoma	1.5	1.0	0.5	1.6	0.6	1.0
10	53	M	R	Jan 16, 1997	15	Carotid operation	2.0	1.5	0.5	3.0	2.2	0.8
11	66	M	L	Mar 3, 1997	15	Lung carcinoma	3.0	2.0	1.0	3.0	0.7	2.3
12	48	M	L	Mar 7, 1997	15	Lung carcinoma	2.0	1.5	0.5	1.4	1.0	0.4
13	44	M	L	Apr 22, 1997	15	Thoracotomy	3.0	2.5	0.5	2.8	1.9	0.9
14	68	F	L	Apr 25, 1997	13	Craniotomy	2.0	1.5	0.5	2.2	0.8	1.4
15	40	M	L	May 26, 1997	15	Lung carcinoma	1.0	1.0	0.0	1.4	1.1	0.3
16	55	F	L	June 17, 1997	13	Thoracotomy	1.5	1.5	0.0	1.2	1.0	0.2
17	70	M	L	June 30, 1997	15	Lung carcinoma	3.0	1.5	1.5	3.0	1.5	1.5
18	36	F	L	July 22, 1997	13	Thyroidectomy	2.0	1.5	0.5	1.6	1.2	0.4
19	53	F	R	Aug 1, 1997	13	Thyroidectomy	2.0	2.0	0.0	1.8	1.8	0.0
20	46	F	L	Sept 17, 1997	15	Thyroidectomy	1.5	1.0	0.5	1.8	1.4	0.4
Median	52.0						2.0	1.5	0.5	1.8	1.1	0.8
Mean	55.6						2.0	1.4	0.6	2.0	1.1	0.9
SD	13.49						0.71	0.48	0.55	0.69	0.51	0.55
								$p < .0001$			$p < .0001$	

the Wilcoxon signed ranks test.

The surgical technique is as follows. Preoperative medication (eg, midazolam hydrochloride), single-dose intravenous cortisone (150 to 250 mg prednisolone hemisuccinate natrium), and a broad-spectrum antibiotic for single-dose prophylaxis are administered approximately 30 minutes preoperatively. Continuous intraoperative propofol administration and patient monitoring are performed by the anesthesiologist.

After infiltration with lidocaine hydrochloride 1% plus epinephrine hydrogen tartrate 1/200,000, a skin incision is made at the level of the mid–thyroid ala, and the thyroid is exposed with the perichondrium preserved. A reference line is drawn parallel to the inferior margin of the thyroid, starting at the midpoint between the superior and inferior thyroid notches (Fig 2[28]). This line divides the distance be-

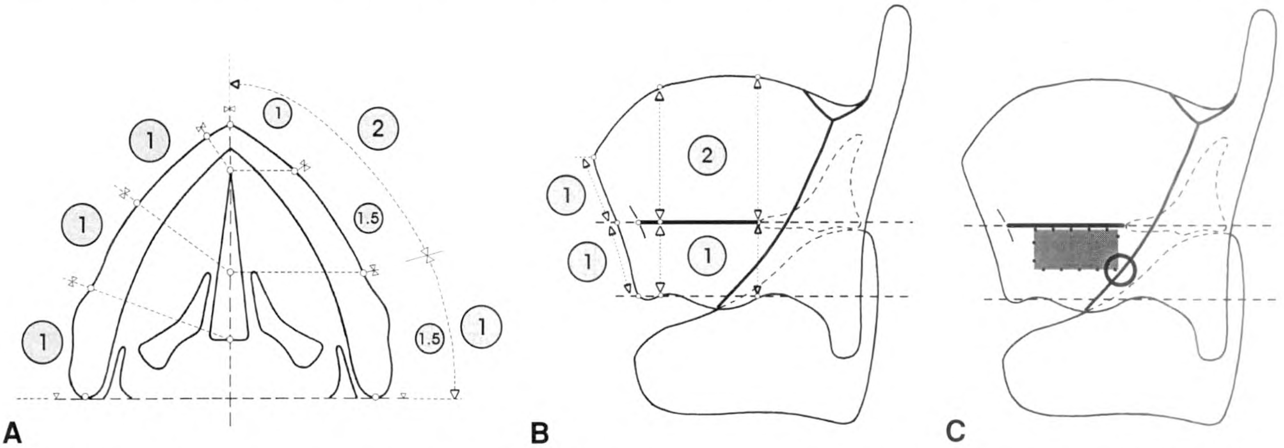


Fig 2. Proportions of larynx and anatomic landmarks for positioning cartilage window (based on study by Friedrich and Lichtenegger[28]). A) Projection of endolaryngeal structures onto thyroid cartilage surface. Lateral projection on right-hand side, perpendicular to thyroid plate on left-hand side. B) Localization of free margin of vocal fold in lateral projection. C) Positioning of cartilage window by using projection of free margin of vocal fold and oblique line (circle).

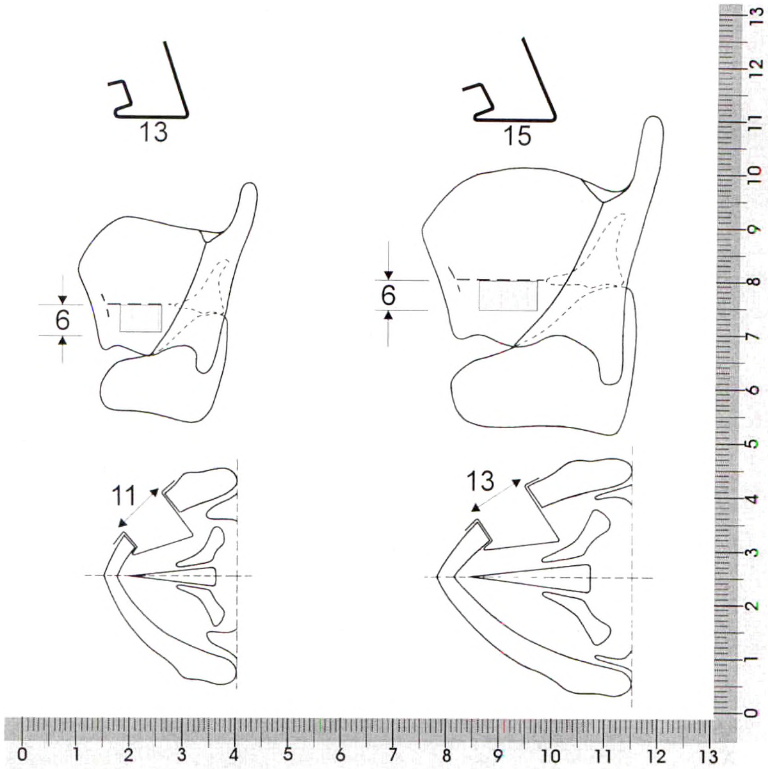


Fig 3. Scale model in millimeters of average male and female thyroid cartilage configurations (based on study by Friedrich and Lichtenegger[28]). Location of cartilage window and correct positioning of 13-mm and 15-mm TVFMIs, respectively.

tween the upper and inferior margins of the thyroid 2:1 and corresponds to the free margin of the vocal folds in the endolarynx.[7,28] Another important landmark for positioning the window is the oblique line. The cartilage window should be placed caudal to the reference line, and the inferior-posterior corner of the window near the oblique line[7] (Figs 2 and 3[28]). For the 13-mm implant (usually used in women), the window size is 6 × 11 mm; for the 15-mm implant (usually used in men), it is 6 × 13 mm (Fig 3).

After outlining the window, the cartilage and osteoid material are drilled out with a steel drill until the inner perichondrium becomes visible (Fig 4). Irrigation with local anesthetics avoids the sensation of pain during surgery and minimizes hemorrhage and edema. After reaching the inner perichondrium, the edges and corners of the window are drilled out with a small diamond bur. The inner perichondrium is incised along the dorsal rim and also partially on the inferior and superior rims with a low-energy electrosurgical knife. It is very important to dissect only the fibrous tissue of the perichondrium, without entering the paraglottic space or cutting the endolaryngeal vessels.

Ventrally, a subperichondrial pocket is created. The dorsal flange of the TVFMI is grasped with a hemostat and the implant is inserted ventrally first (Figs 4 and 5). The basal plate of the TVFMI is 2 mm larger than the cartilage window. The implant must therefore be slightly bent with the hemostat and a finger of the contralateral hand. This enables the implant to be introduced under slight tension through the cartilage window into the endolarynx. The optimal medialization depth is then determined by pressing the TVFMI in and marking the location with the hemostat. The dorsal flange is bent at the level of this mark in the dorsal direction, and the TVFMI is fixated with 2 sutures of monophilic nonabsorbable thread (Figs 5 and 6). Because of the special design of the TVFMI, no special attachment procedures are required in the ventral section.

RESULTS AND DISCUSSION

With the increasing worldwide spread of the Isshiki technique[1,2] for external vocal fold medialization, disadvantages and limitations of the method have emerged, and an increasing demand for a ready-made and standardized implant system has been observed.[4,12,13] The aim of this study was to develop a simple and efficient implant system that not only allows an uncomplicated and time-saving application, but also ensures good, stable, and reproducible functional results. Maximal safety for the patients should be guaranteed by using the safest possible material with the highest degree of stabilization and fixation of the implant.

I decided to use medical-grade titanium ASTM F67, which has the particular advantage of proven biocompatibility in over 100,000 applications of

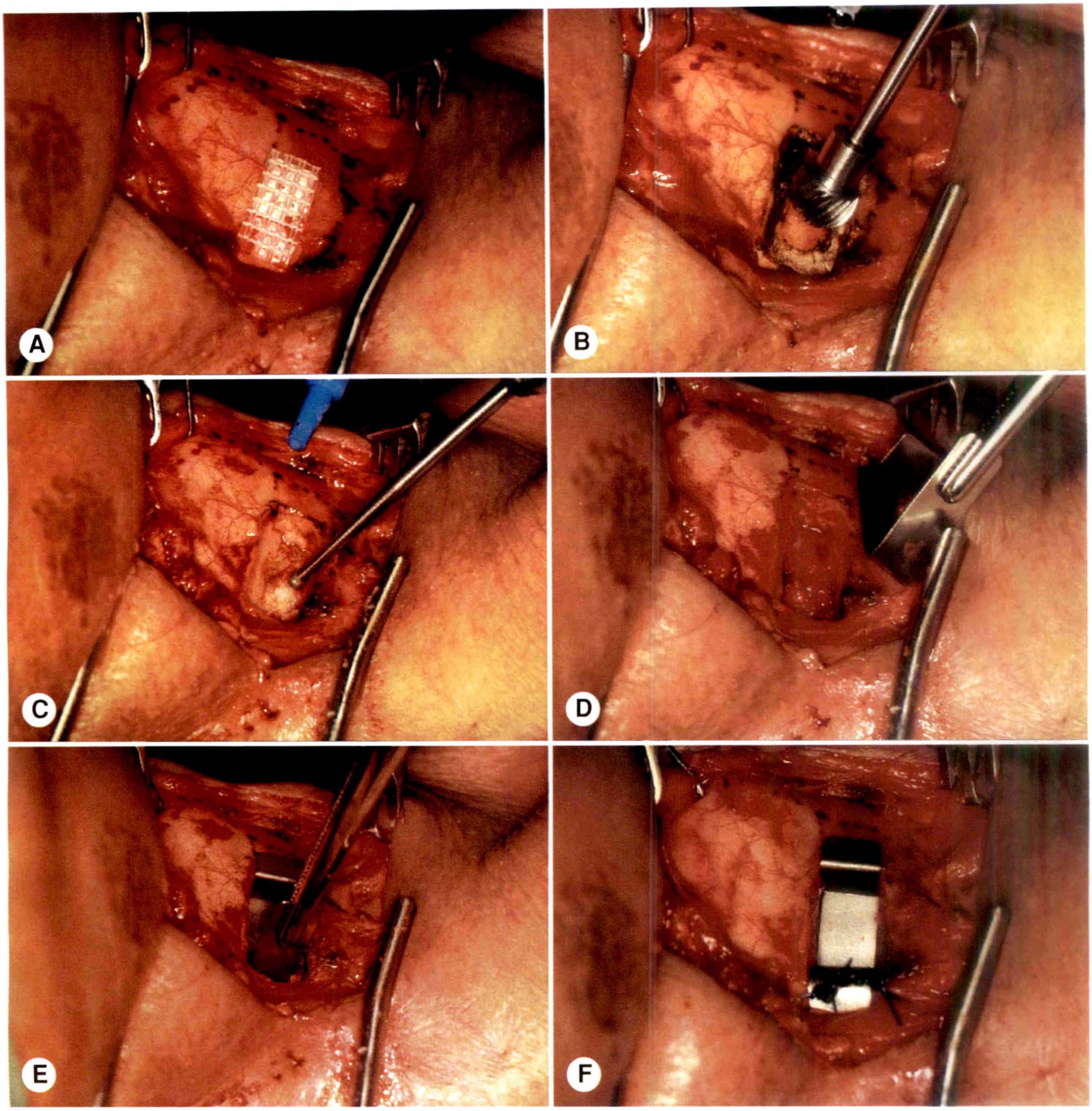


Fig 4. Vocal fold medialization using TVFMI. A) Positioning window with template made out of silicone sheet. B) Drilling out outlined window. C) Using diamond bur and irrigation with local anesthetics near inner perichondrium. D,E) Inserting TVFMI. F) Fixation with sutures.

heart surgery, joint endoprostheses, and maxillofacial, mastoid, and laryngotracheal surgery.[16,29-33] A titanium sheet of 0.25-mm thickness and ASTM grade 4 quality turned out to have an appropriate balance of stiffness and elasticity (Fig 1). After overcoming the first elastic stage of bending, the titanium sheet can be permanently changed in shape. To avoid breaking, bending should be limited to a single procedure, and sharp-angled bending should be omitted by using customized bending pliers. Titanium is nonferromagnetic and so does not interfere with magnetic resonance imaging or computed tomography. The implant can be localized precisely by X-ray and computed tomographic scan examination if needed (Fig 7). Irradiation with microwaves should in general not be used in patients receiving a metal implant.

Essential for the success of the operation is the optimal positioning of the implant, determined by the proper localization of the cartilage window.[7] As shown in a former study, the relative proportions of the thyroid are fairly constant and not gender-specific, in contrast to the absolute dimensions[28] (Fig 2).

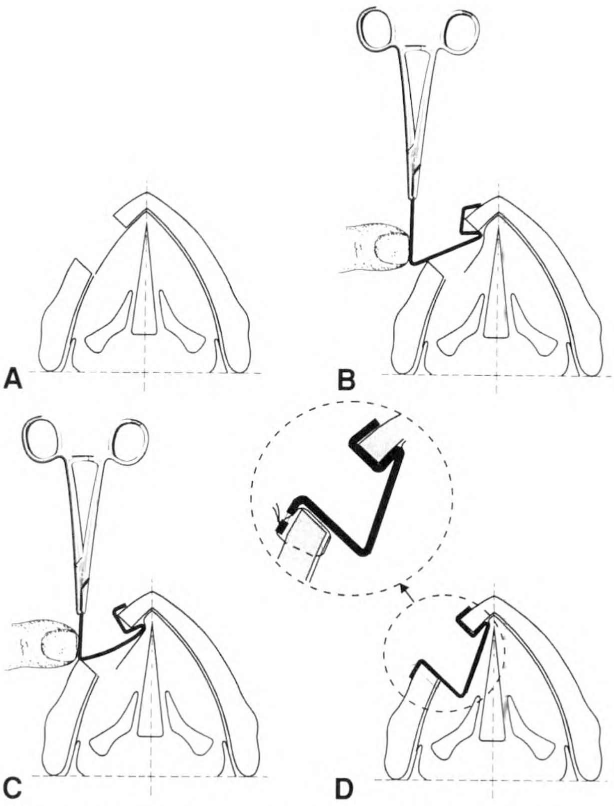


Fig 5. Inserting TVFMI (schematic). A) Situation after excision of cartilage and incision of inner perichondrium at dorsal rim. B) Inserting TVFMI ventrally. C) Introducing TVFMI into endolarynx with slight tension. D) TVFMI correctly inserted and fixated with sutures dorsally.

It seems therefore appropriate to use the relative proportions for clinical purposes, instead of absolute dimensions. The midpoint between the superior and inferior thyroid notches corresponds to the endolaryngeal insertion of Broyles' tendon. Starting at this point, the free margin of the vocal folds projects parallel to the inferior border of the thyroid.[7,28] This line divides the distance between the upper and inferior margins of the thyroid 2:1 (Fig 2B). In order to avoid a bulging of the ventricular fold, the window should be positioned caudal to this reference line, leaving 3 to 4 mm of cartilage intact to avoid a fracture of the inferior thyroid rim[2,7] (Fig 3).

The dorsoventral positioning determines the maximal medialization along the free margin of the vocal folds. Positioning too far anterior can cause an unintended overadduction in the ventral portion of the vocal folds and should therefore be avoided.[7,14,23] An important landmark for this positioning is the oblique line. According to my investigations, the tip of the vocal process projects just anterior to the oblique line in a lateral projection[28] (Fig 2). The inferior-posterior corner of the cartilage window should be placed in the area of the oblique line (Figs 2 and 3). I therefore prefer to position the window further dorsal than is recommended by Isshiki.[6] According to our investigations and clinical experience, there is little danger of interfering with the upper rim of the cricoid.[6,28] Considering these landmarks, an optimal implant position can be achieved with the posterior edge of the TVFMI located lateral to the vocal process, resulting in a physiologic medialization of the entire vocal fold[7] (Figs 3 and 7).

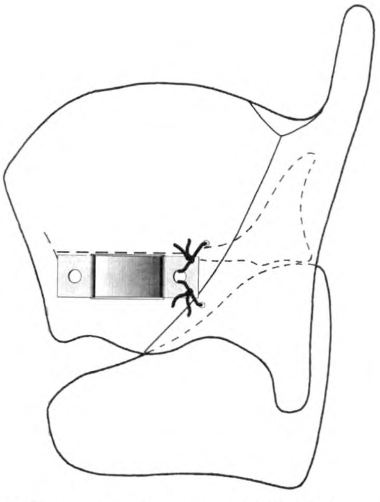


Fig 6. Fixation with sutures of TVFMI in situ.

In contrast to Isshiki,[1,2,6] I recommend drilling out the cartilage to allow an atraumatic and time-saving preparation under optimal visibility (Fig 4). In this manner, injuries to the endolaryngeal tissue and vessels can be avoided and hemostasis can be obtained precisely. In addition, there is little danger of dislocation, resorption, or regeneration of the remaining cartilage island.[5,7,12-14,25] Extrusion of the implant, stated by some authors to be a possible complication after removal of the cartilage,[1,2,6,11,23] is not to be feared, due to the relatively safe fixation of the TVFMI. The TVFMI is also suitable for medialization according to the Isshiki procedure without removing the cartilage. We used this technique in patient 8 after a cordectomy in order to minimize the danger of perforation due to the thin endolaryngeal scar tissue. In accordance with other authors,[12-14] I

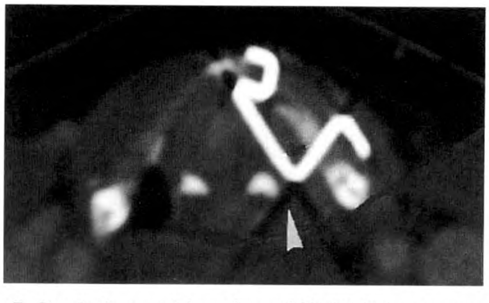


Fig 7. Depiction and location of TVFMI by computed tomography scan. Optimal position of implant is shown, with posterior edge lateral to vocal process (arrowhead).

also found that incising the perichondrium at the posterior edge of the window eases the medialization and spares mobilization.

Due to the special design, the TVFMI is simple to handle and self-locking anteriorly because of its U-shape. The degree of medialization is determined easily by pressing the posterior part of the TVFMI inward (Figs 4 and 5). After determining the optimal medialization depth, the dorsal flange of the TVFMI is bent and a relatively safe fixation is ensured dorsally with 2 monophilic nonabsorbable sutures. An alternative would be the use of special cartilage screws, if they were commercially available.[30,31] Bone screws will not guarantee a stable fixation and cannot be recommended.[7]

In contrast to other commercially available implant systems,[4,12] which consist of numerous different sizes and shapes of implants, I consider 2 sizes of the TVFMI to be sufficient for medialization. The 13-mm implant is used in the smaller (normally female) larynx, and the 15-mm implant in the larger (normally male) larynx. The cartilage window is cut approximately 2 mm smaller (ie, 11 × 6 mm and 13 × 6 mm), so that the TVFMI has to be inserted under slight tension (Figs 3 and 5). In the endolarynx, it expands, thus snapping into place and stabilizing its position automatically. I consider it an additional advantage of the TVFMI that no special and expensive instrumentation is required for insertion. Only simple bending pliers are recommended for bending the implant in order to avoid fracture. All other instruments are standard in every otolaryngological operating room.

Experience on my first 20 patients revealed no surgical problems or perioperative complications in any case (Table 2). The major advantage was a significantly reduced operation time due to the preformed implant. This is not only more convenient for both the surgeon and the patient, but is also critical for obtaining optimal results, due to the reduced intralaryngeal swelling and hematoma.[4,10,20]

The reduction of the glottic gap by the operation is statistically significant (Table 2). Up to now, I have experienced no sign of complications and/or suboptimal implant positioning such as dislocation, ventral overadduction, bulging of the ventricular folds, change in vocal fold position, or underadduction.[7] Significant improvement of all voice parameters was achieved and demonstrated by a statistically significant reduction of the voice dysfunction index.[8] Due to the limited follow-up period, the results cannot be considered definitive, but are in accordance with my previously published results and statements in the literature.[7,8]

CONCLUSIONS

Clinical results show evidence that an external vocal fold medialization with the TVFMI can be performed easily and without complications. The functional short-term results are in accordance with my previous experience and statements in the literature.[7,8] Compared to the current techniques and implant systems, I see the following additional advantages.

1. Titanium is a relatively safe implant material with excellent biocompatibility.
2. The design ensures an optimal fixation and stabilization, thus minimizing the danger of dislocation.
3. The implantation technique and handling are simple and time-saving, thus shortening the operation time and improving the results.
4. The titanium sheet is easy to shape and adapt to the individual situation.
5. Only 2 sizes of implants are required, and no expensive instruments. The TVFMI is thus economical.

ACKNOWLEDGMENT — Printing of the color illustrations has been made possible by support from the Heinz Kurz Company, Dusslingen, Germany. The author expresses his appreciation for this support.

REFERENCES

1. Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. Acta Otolaryngol (Stockh) 1974;78:451-7.

2. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol (Stockh) 1975;80:465-73.

3. Payr E. Plastik am Schildknorpel zur Behebung der Folgen einseitiger Stimmbandlähmung [Thyroplasty in treatment of unilateral vocal fold paralysis]. Dtsch Med Wochenschr 1915; 43:1265-70.

4. Cummings CW, Purcell LL, Flint PW. Hydroxylapatite laryngeal implants for medialization. Preliminary report. Ann Otol Rhinol Laryngol 1993;102:843-51.

5. Harries ML, Morrison M. Short-term results of laryngeal framework surgery. Thyroplasty type 1: a pilot study. J Otolaryngol 1995;24:281-7.

6. Isshiki N. Phonosurgery: theory and practice. Tokyo, Japan: Springer, 1989.

7. Friedrich G. Externe Stimmlippenmedialisation: Operative Erfahrungen und Modifikationen [External vocal fold medialization: surgical experience and modification]. Laryngorhinootologie 1998;77:7-17.

8. Friedrich G. Externe Stimmlippenmedialisation: Funktionelle Ergebnisse [External vocal fold medialization: func-

tional results]. Laryngorhinootologie 1998;77:18-26.

9. Koufman JA. Laryngoplasty for vocal cord medialization: an alternative to Teflon. Laryngoscope 1986;96:726-31.

10. Koufman JA. Laryngoplastic phonosurgery. In: Johnson J, ed. Instructional courses, American Academy of Otolaryngology–Head and Neck Surgery. Vol 1. St. Louis, Mo: Mosby, 1988: 339-50.

11. Mahieu HF, Schutte HK. New surgical techniques for voice improvement. Arch Otorhinolaryngol 1989;246:397-402.

12. Montgomery WW, Blaugrund SM, Varvares MA. Thyroplasty: a new approach. Ann Otol Rhinol Laryngol 1993;102: 571-9.

13. Montgomery WW, Montgomery SK. Montgomery® Thyroplasty Implant System. Ann Otol Rhinol Laryngol Suppl 1997;106(suppl 170).

14. Wanamaker JR, Netterville JL, Ossoff RH. Phonosurgery: Silastic medialization for unilateral vocal fold paralysis. Operative Techniques Otolaryngol Head Neck Surg 1993; 4:207-17.

15. Hunsaker DH, Martin PJ. Allergic reaction to solid silicone implant in medial thyroplasty. Otolaryngol Head Neck Surg 1995;113:782-4.

16. Berghaus A. Alloplastische Implantate in der Kopf-Halschirurgie [Alloplastic implants in head and neck surgery]. Eur Arch Otorhinolaryngol 1992(suppl 1):53-95.

17. Desrosiers M, Ahmarani C, Bettez M. Precise vocal cord medialization using an adjustable laryngeal implant: a preliminary study. Otolaryngol Head Neck Surg 1993;109:1014-9.

18. Sakai N, Nishizawa N, Matsushima J. Thyroplasty type I with ceramic shim. Jpn Artif Organs 1996;20:951-4.

19. McCulloch TM, Hoffman HT. Medialization laryngoplasty with expanded polytetrafluoroethylene. Surgical technique and preliminary results. Ann Otol Rhinol Laryngol 1998; 107:427-32.

20. Isshiki N, Taira T, Kojima H, Shoji K. Recent modifications in thyroplasty type I. Ann Otol Rhinol Laryngol 1989;98: 777-9.

21. Flint PW, Corio RL, Cummings CW. Comparison of soft tissue response in rabbits following laryngeal implantation with hydroxylapatite, silicone rubber, and Teflon. Ann Otol Rhinol Laryngol 1997;106:399-407.

22. Cotter CS, Avidano MA, Crary MA. Laryngeal complications after type I thyroplasty. Otolaryngol Head Neck Surg 1995; 113:671-3.

23. Ford CN, Bless DM, Prehn RB. Thyroplasty as primary and adjunctive treatment of glottic insufficiency. J Voice 1992;6: 277-85.

24. Tucker HM, Wannamaker J, Trott M. Complications of laryngeal framework surgery (phonosurgery). Laryngoscope 1993;103:525-8.

25. Sasaki CT, Driscoll BP, Gracco C, Eisen R. The fate of medialized cartilage in thyroplasty type I. Arch Otolaryngol Head Neck Surg 1994;120:1398-9.

26. Friedrich G. Qualitätssicherung in der Phoniatrie. Vorschlag zur Standardisierung der Klinischen Stimmprüfung [Quality assurance in phoniatrics. Suggestion for standardization of clinical voice diagnosis]. HNO 1996;44:401-16.

27. Van Lierde K, Moerman M, Vermeersch H, Van Cauwenberge P. An introduction to Computerized Speech Lab. Acta Otorhinolaryngol Belg 1996;50:309-14.

28. Friedrich G, Lichtenegger R. Surgical anatomy of the larynx. J Voice 1997;11:345-55.

29. Branemark PJ, Hansson B, Adell R, Breine U. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10 years period. Scand J Plast Reconstr Surg 1977; 16:1-132.

30. Siegert R, Merz H, Malisius R, Ahrens KH, Weerda H. Histopathology of laryngeal changes after long-term chondrosynthesis. Eur Arch Otorhinolaryngol 1997;254:463-5.

31. Siegert R, Zimmermann E, Oppermann P, Remmert S, Ahrens K-H, Weerda H. Experimental and clinical evaluation of laryngeal chondrosynthesis. Eur Arch Otorhinolaryngol 1996; 253:481-7.

32. Steinhart H, Schroeder HG. Müssen Osteosyntheseplatten im Gesichtsschädelbereich wieder entfernt werden [Is it necessary to remove osteosynthetic material after facial bone osteosynthesis]? HNO 1995;43:211-5.

33. Woo P, Kellman R. Laryngeal framework reconstruction with miniplates: indication and extended indications in 27 cases. Operative Techniques Otolaryngol Head Neck Surg 1992;3:159-64.

Ann Otol Rhinol Laryngol 108:1999

CAROTID ARTERY OCCLUSION DUE TO BACTERIAL PARANASAL SINUSITIS

MEHMET ZİYA ÖZÜER, MD
FAZIL NECDET ARDIÇ, MD
ERDAL COSKUN, MD
A. NEVZAT YALÇIN, MD
NURAN SABİR AKKOYUNLU, MD
DENİZLİ, TURKEY

Complications of paranasal sinusitis still continue to be a serious health problem. We present an orbita-related complication of sinusitis in a patient with diabetic ketoacidosis. It was not a rhinocerebral mucormycosis, but a bacterial sinusitis–induced development of left cavernous sinus thrombophlebitis and carotid artery occlusion. We discuss the diagnosis, surgical options, and clinical outcome.

KEY WORDS — carotid artery occlusion, cavernous sinus thrombophlebitis, computed tomography, paranasal sinusitis.

INTRODUCTION

Complicated paranasal sinus infections are rare, but still occur and cause life-threatening problems, especially in diabetic and immunocompromised hosts. They require prompt diagnosis and intervention in order to avoid possible mortal consequences. Orbital involvement has been reported in approximately 3% of patients with sinusitis.[1] Dehiscence of the lamina papyracea and valveless ophthalmic veins facilitate spreading of the infection. We present a patient with paranasal sinusitis and orbital involvement, without mucormycosis, who had diabetic ketoacidosis.

CASE REPORT

A 27-year-old man was admitted to the emergency room with severe persistent frontal headache and loss of vision in his left eye that occurred over a period of 24 hours. He had had type I diabetes mellitus for 6 years. On physical examination, his fever was 38°C, and he had left proptosis with chemosis and periorbital swelling. Eye examination revealed no light perception and limited movement of the left eye. Fundoscopic examination showed venous stasis–like retinal changes. There was mucopurulent discharge in the middle and inferior meatus. Otherwise, the findings of the neurologic examination were normal. Laboratory investigations revealed leukocytosis; the fasting blood glucose was 393 mg/dL, and a urine examination showed (+++) glucose. No sign of orbital apex involvement was present. Computed tomography (CT) demonstrated inflammatory changes in the left ethmoid cells, while the sphenoid sinuses were within normal limits (Fig 1). Magnetic resonance imaging revealed diffuse inflammatory changes in the ethmoid cells, minimal mucosal thickening within the left maxillary and frontal sinuses, and increased left retrobulbar fat space. No sign of optic nerve or extraocular muscle involvement was present. Both the left cavernous sinus and the left carotid artery (cavernous and supraclinoid parts) were within normal limits (Fig 2A).

Immediate external sphenoethmoidectomy was performed. During surgery, excessive edema with

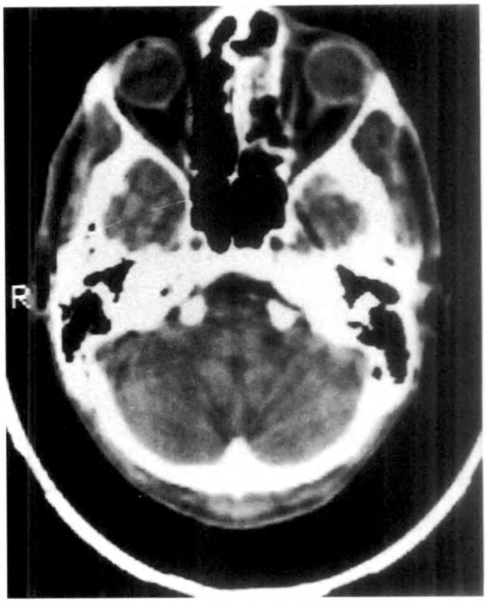


Fig 1. Preoperative computed tomography. Demonstrates inflammatory changes in left ethmoid cells, while sphenoid sinuses were within normal limits.

From the Departments of Otolaryngology–Head and Neck Surgery (Özüer, Ardiç), Neurosurgery (Coskun), Infectious Diseases (Yalçin), and Radiology (Akkoyunlu), Pamukkale University, School of Medicine, Denizli, Turkey.
CORRESPONDENCE — Mehmet Ziya Özüer, MD, Çamlık mah. 2595 sok. 15/8, Denizli 20020, Turkey.

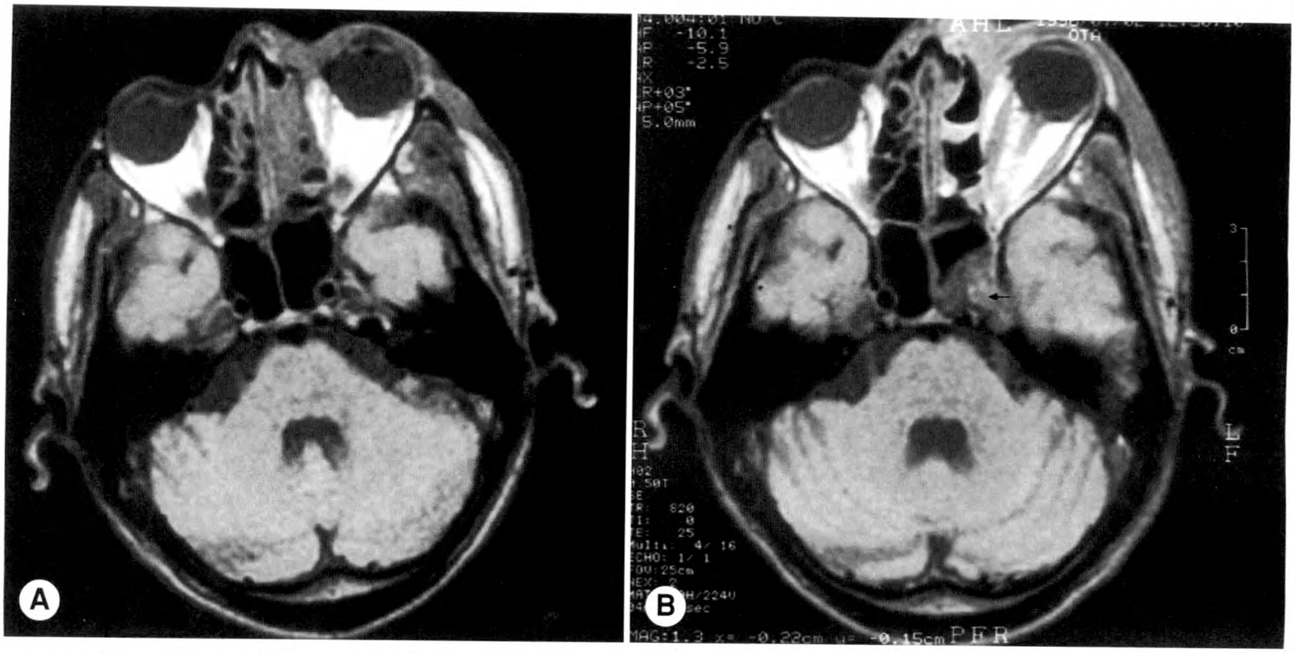


Fig 2. T1-weighted axial magnetic resonance images. A) Preoperative. Demonstrates left periorbital cellulitis, orbital proptosis, and diffuse inflammatory changes in left ethmoid cells. Both left cavernous sinus and left carotid artery are within normal limits. B) Postoperative, on seventh day. Demonstrates marked expansion of left cavernous sinus, and occlusion of cavernous and supraclinoid parts of left internal carotid artery (arrow).

polypoid inflammation in the ethmoid cells was noted. Creating a large bony window at the anterior sphenoidal wall was not intended; instead, widening of the natural ostium enabled telescopes to be passed through and the sphenoid sinus to be inspected with enhanced visualization. No sign of mucosal inflammation in the sphenoid sinus was encountered. Fungal stains were negative. Gram's stain showed gram-positive cocci in clusters. Early cultures revealed no fungal or bacterial growth. No visual acuity change was noted in the postoperative period. Medical treatment consisted of sulbactam-ampicillin 1 g intravenously 4 times per day; regular insulin 18 U 3 times per day; acetyl salicylate 300 mg/d orally; and dipyridamole 75 mg orally 3 times per day. *Klebsiella pneumoniae* was cultured from nasal mucopurulence on the fourth postoperative day and gentamicin 240 mg/d intramuscularly was also commenced.

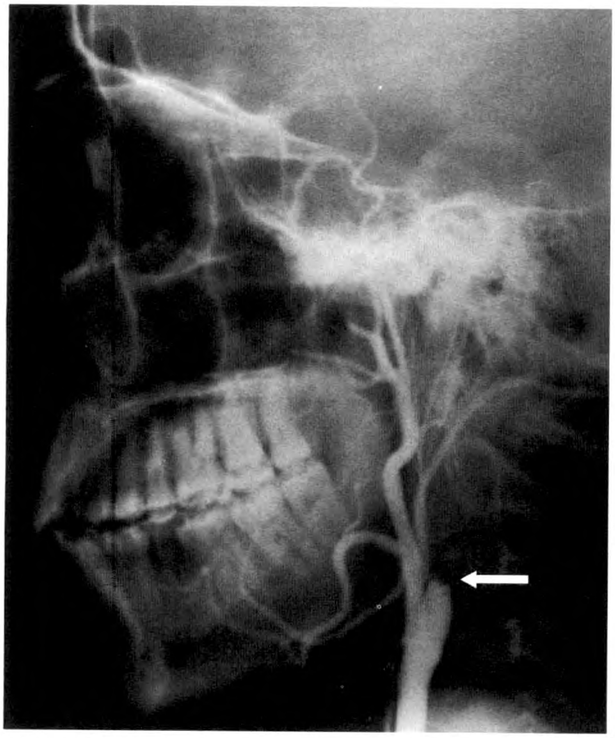


Fig 3. Occlusion of left internal carotid artery distal to bifurcation (arrow), noted following direct injection of contrast agent into left common carotid artery.

On the seventh postoperative day, right hemiparesis developed. Magnetic resonance imaging demonstrated marked left cavernous sinus fullness with convexity of the lateral margin; the sphenoid sinus on the involved side showed soft tissue involvement that was not present in the former imaging study (Fig 2B). A T2-weighted series showed hyperintense acute ischemic changes. The left carotid artery showed occlusion of the cavernous and supraclinoid parts. Full left carotid artery occlusion distal to the bifurcation was noted on angiographic examination (Fig 3). Supportive measures were taken in addition to the medical therapy, including oral methylprednisolone 16 mg/d with gradual tapering. The patient was discharged on the 40th day with a residual right hemiparesis. There was slight improvement in the right hemiparesis 9 months later.

DISCUSSION

Complications of paranasal sinus infections may arise despite serious treatment and remain to be a health problem. Early diagnosis and meticulous treatment is the hallmark of management, especially in diabetic and immunocompromised hosts.[2,3] Any patient with loss of vision and restricted extraocular mobility requires prompt surgical intervention. Cavernous sinus thrombophlebitis (CST) is the most severe consequence of postseptal cellulitis. It is the extension of disease via valveless veins between the orbit and the cavernous sinus. Though it presents initially unilaterally, bilateral signs may evolve. Obstruction of the superior orbital vein induces proptosis, chemosis, and orbital edema. In addition, palsy of cranial nerves III, IV, or VI may occur.[4,5] Dilatation of episcleral veins may be noted.[6] This constellation of findings should always alert the physician.

Diabetics constitute a huge group of immunocompromised hosts. Diabetic patients have deficient suppressor T cell function, especially in the early period of the illness.[7] Decreased phytohemagglutinin stimulation of lymphocytes and chemotaxis and poor bacterial ingestion have been demonstrated in diabetic patients.[8] Nasopharyngeal colonization with *Staphylococcus aureus* occurs with increased frequency in diabetic patients on insulin therapy.[7]

Rhinocerebral mucormycosis, which is often a fatal fungal infection, should be considered in the differential diagnosis.[5,9,10] Our patient lacked the black necrotic eschar on the concha, palate, and face. Clinically, we did not have a sign of rhinocerebral mucormycosis; however, we reconsidered it when the carotid artery occlusion occurred. However, repeated biopsy specimens demonstrated no hyphae, and cultures showed no fungal growth.

Occurrence of CST on the seventh postoperative day could be attributed to ineffective surgery; however, it is more compatible with immunocompromised status. A secondary invasion of the sphenoid sinus after surgery might give way to CST.

According to Kriss et al,[5] the role of anticoagulant therapy is still a subject of debate in CST. Sofferman[11] does not recommend anticoagulant therapy in the absence of emboli or progressive thrombophlebitis. Levine et al[4] reported no statistical change in mortality rates when early heparin was not commenced; we did not introduce early heparin. Steroid therapy in CST is also controversial. Some authors found no benefit to steroids in the treatment of CST.[5] Levine et al[4] found them effective in cranial nerve dysfunction. Adjunctive corticosteroids have been recommended in therapy.[12] Our patient received 16 mg/d methylprednisolone with decreasing dosage for 8 days.

According to Stammberger and Hawke,[13] endoscopic paranasal sinus surgery could also be used in orbital complications of acute sinusitis. Stankiewicz et al[14] consider endoscopic surgery more problematic in these patients because of the acute infection that causes increased bleeding and decreased visualization. External sphenoethmoidectomy was the surgical intervention performed in our case. We concluded that the external route might be the preferred procedure, as it is less time-consuming and easily performed and does not require skilled surgery. Besides, the expected complication incidence is lower in a complicated paranasal sinusitis.

To the best of our knowledge, survival after CST and carotid artery occlusion due to paranasal sinusitis other than mucormycosis is not reported in the English-language literature. According to Moll et al[9] and Cheung et al,[15] carotid artery occlusion is, rather, a complication of rhinocerebral mucormycosis in diabetic ketoacidosis. Our case differs in this respect from the literature, showing that not only fungi, but also bacterial microorganisms, can induce carotid artery occlusion as a consequence of severe paranasal sinus complications.

REFERENCES

1. Oliverio PJ, Benson ML, Zinreich SJ. Update on imaging for functional endoscopic sinus surgery. Otolaryngol Clin North Am 1995;28:585-608.

2. Clayman GL, Adams GL, Paugh DR, Koopmann CF. Intracranial complications of paranasal sinusitis: a combined institutional review. Laryngoscope 1991;101:234-9.

3. Slavin ML, Glaser JS. Acute severe irreversible visual loss with sphenoethmoiditis–posterior orbital cellulitis. Arch Ophthalmol 1987;105:345-8.

4. Levine SR, Twyman RE, Gilman S. The role of anticoagulation in cavernous sinus thrombosis. Neurology 1988;38:517-22.

5. Kriss TC, Kriss VM, Warf BC. Cavernous sinus thrombophlebitis: case report. Neurosurgery 1996;39:385-9.

6. Moloney JR, Badham NJ, McRae A. The acute orbit preseptal (periorbital) cellulitis, subperiosteal abscess and orbital cellulitis due to sinusitis. J Laryngol Otol Suppl 1987(suppl 12):1-18.

7. Chow AW. Infections of the oral cavity, neck and head. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. New York, NY: Churchill Livingstone, 1995:593-606.

8. Gallacher SJ, Thomson G, Fraser WP, Fisher BM, Gemmell CG, MacCuish AC. Neutrophil bactericidal function in diabetes mellitus: evidence for association with blood glucose control. Diabet Med 1995;12:916-20.

9. Moll GW, Liu GC, Raila FA, Conerley AW. Rhinocerebral mucormycosis in IDDM. Diabetes Care 1994;17:1348-53.

10. Galetta SL, Wulc AE, Goldberg HI, Nichols CW, Glaser JS. Rhinocerebral mucormycosis: management and survival after carotid occlusion. Ann Neurol 1990;28:103-7.

11. Sofferman RA. Cavernous sinus thrombophlebitis secondary to sphenoid sinusitis. Laryngoscope 1983;93:797-800.

12. Clifford-Jones RE, Ellis CJK, Stevens JM. Cavernous sinus thrombosis. J Neurol Neurosurg Psychiatry 1982;45:1092-6.

13. Stammberger H, Hawke M. Essentials of functional endoscopic sinus surgery. St Louis, Mo: Mosby, 1993:131-8.

14. Stankiewicz JA, Park AA, Newell DJ. Complications of sinusitis. Curr Opin Otolaryngol Head Neck Surg 1996;4:17-20.

15. Cheung SW, Lee KC, Cha IC. Orbitocerebral complications of pseudomonas sinusitis. Laryngoscope 1992;102:1385-9.

≈

MIDDLE EAR MECHANICS

The Second International Symposium on Middle Ear Mechanics in Research and Otosurgery will be held October 21-24, 1999, in Boston, Massachusetts. For information, contact Harvard MED-CME, PO Box 825, Boston, MA 02117; telephone (617) 432-1525; web site http://www.med.harvard.edu/conted/.

IMAGING CASE STUDY OF THE MONTH

BROWN TUMOR OF THE PALATE IN A PATIENT WITH PRIMARY HYPERPARATHYROIDISM

SHAUN N. SCOTT, MD
YUTAKA SATO, MD
SCOTT M. GRAHAM, MD
ROBERT A. ROBINSON, MD, PHD
IOWA CITY, IOWA

INTRODUCTION

The manifestation of primary hyperparathyroidism as skeletal disease has nearly disappeared in the last 2 decades. Cases are now most often diagnosed by the incidental finding of asymptomatic hypercalcemia. Improved screening techniques have made clinical evidence of bone disease uncommon. Classic radiographic findings of subperiosteal bone resorption, bone cysts, brown tumors, and generalized osteopenia now occur in fewer than 5% of cases.[1-3] Brown tumors may occur in the head and neck, with the mandible being the most frequent site. Involvement of the maxilla is exceptionally rare.[4,5]

A brown tumor most commonly presents as a slowly enlarging, painful mass. These tumors can be locally aggressive, but do not possess metastatic potential. Histologically, they are similar to giant cell lesions. Treatment initially focuses on correction of the hypercalcemic state. Brown tumors frequently show regression after normocalcemia is achieved, but surgical resection is necessary in some patients.

We present a case of a brown tumor involving the hard palate and nasal cavity in a young woman.

CASE REPORT

A 23-year-old woman initially presented with a 3-week history of fatigue, generalized weakness, subjective fevers, and intermittent nocturia. Her physical examination findings were within normal limits. Laboratory results revealed an elevated calcium level of 12.9 mg/dL (normal 8.5 to 10.5 mg/dL) and a low phosphorus level of 2.1 mg/dL (normal 2.5 to 4.5 mg/dL). Subsequent testing revealed a parathyroid hormone level of 112 pg/mL (normal 10 to 65 pg/mL). Initial chest radiographs were unremarkable. A diagnosis of primary hyperparathyroidism was suspected.

Six weeks after initial presentation, the patient was evaluated by an endocrinologic surgeon. Her symptoms had persisted, with a worsening of the fatigue and weakness. On physical examination, a 1.5 × 1.0-cm soft tissue swelling of the hard palate was noted. The mass was poorly demarcated and tender on palpation. The mucosal surface overlying the mass had a bluish discoloration. No ulceration was present. There was no cervical lymphadenopathy palpable.

A parathyroidectomy was subsequently performed, demonstrating a right inferior adenoma that weighed 0.8 g. The pathologic specimen, shown in Fig 1, consisted of chief cells arranged in broad bands with intermixed areas of oxyphil cells and water-clear cells. Scattered lamellar calcifications were also present. These findings were consistent with a parathyroid adenoma. The patient's postoperative course was uncomplicated, and she was normocalcemic at the time of discharge.

The hard palate lesion continued to increase in size over the next 2 months. At the time of evaluation in our clinic, 3 months after the palatal lesion was identified, the patient was experiencing progressive right nasal obstruction. Intraoral examination revealed a large submucosal mass of the hard palate that extended posteriorly into the soft palate. The right nasal cavity was completely filled by the mass. The right aspect of the nasopharynx was also partially obstructed. Coronal computed tomography demonstrated a large cystic mass centered in the right nasal cavity. The nasal turbinates were completely obliterated. The mass eroded the right maxillary sinus and, medially, the nasal septum. There was also extension through the hard palate into the oral cavity (Fig 2). Contrast-enhanced scans demonstrated

---

From the Departments of Otolaryngology–Head and Neck Surgery (Scott, Graham), Radiology (Sato), and Pathology (Robinson), The University of Iowa, Iowa City, Iowa.

CORRESPONDENCE — Scott M. Graham, MD, Dept of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, 200 Hawkins Dr, E230 GH, Iowa City, IA 52242.

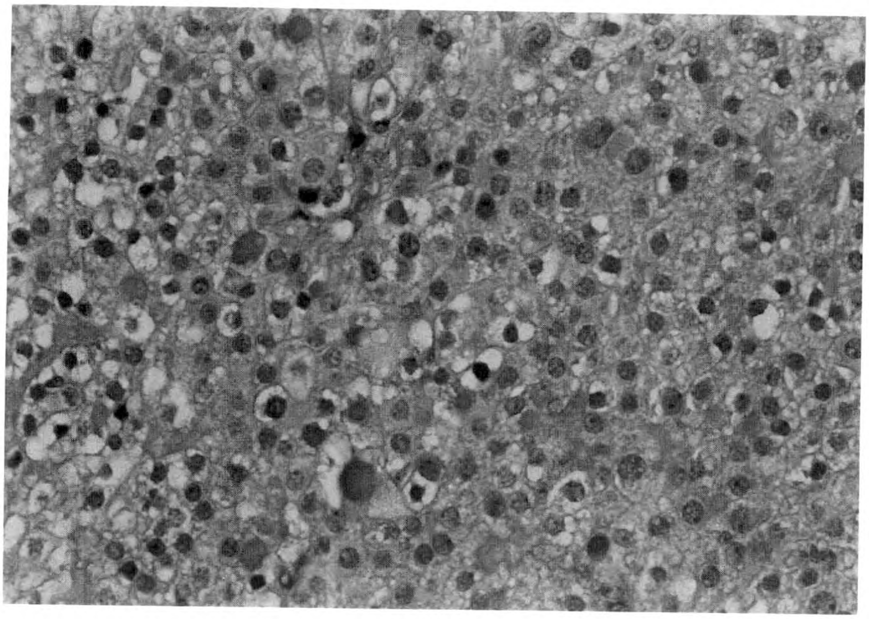


Fig 1. Parathyroid adenoma with mixture of clear and chief cells.

peripheral enhancement, as well as solid areas of uptake within the mass. A Tc99m bone scan showed increased uptake in the right maxillary region and a small nonspecific focus in the right occipital area. The differential diagnrosis entertained at that time included inverting papilloma, squamous cell carcinoma, midline granuloma, ossifying fibroma, lymphoma, and brown tumor.

An endoscopic biopsy demonstrated a fibrous spindle cell population with numerous focal proliferations of multinucleate giant cells. Rare lamellar bone fragments with osteoblastic rimming were also present (Fig 3). These findings were felt to be most consistent with a brown tumor. A giant cell granuloma, ossifying fibroma, or other fibro-osseous process could not be ruled out, however.

The patient underwent a transnasal endoscopic subtotal resection of the mass. There were multiple areas of old hemorrhage surrounding the lobulated, fibrous mass. The nasal septum and right lateral nasal wall were debulked of tumor. The mass was resected from the hard palate, leaving intact the mucoperiosteum on the intraoral aspect.

DISCUSSION

Primary hyperparathyroidism has a changing pattern of clinical presentation. Prior to the mid-1970s, more than 50% of patients with primary hyperparathyroidism had evidence of skeletal or renal disease.[6] During the next decade, biochemical screening tech-

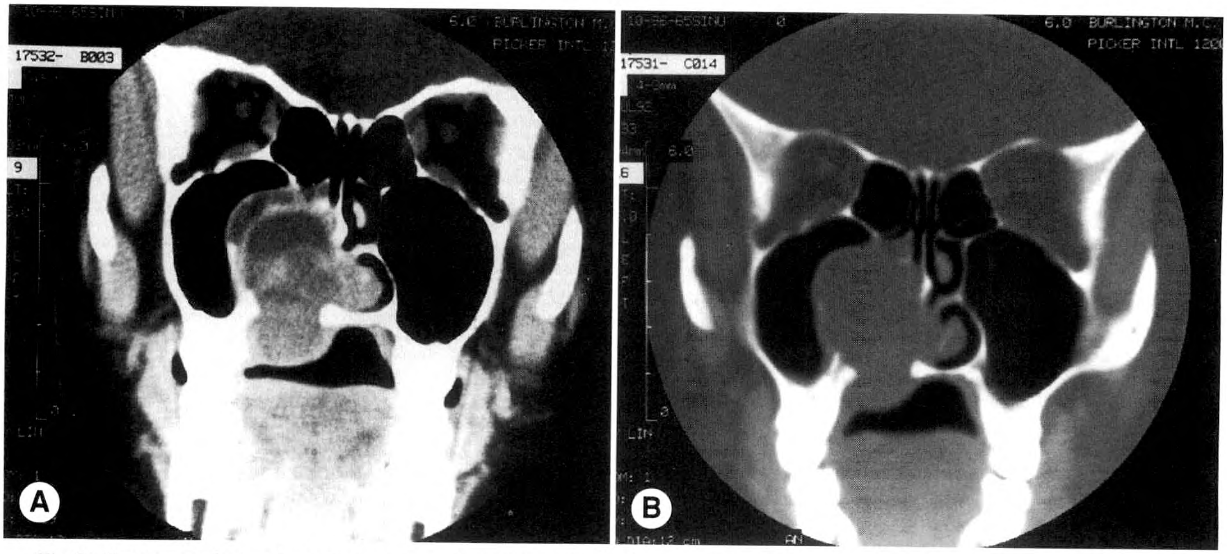


Fig 2. Contrast-enhanced coronal computed tomograms. A) Large cystic mass completely fills right nasal cavity, expanding and eroding right hard palate, nasal septum, and lateral nasal wall. Contrast enhancement is inhomogeneous. B) Same image with wider window setting.

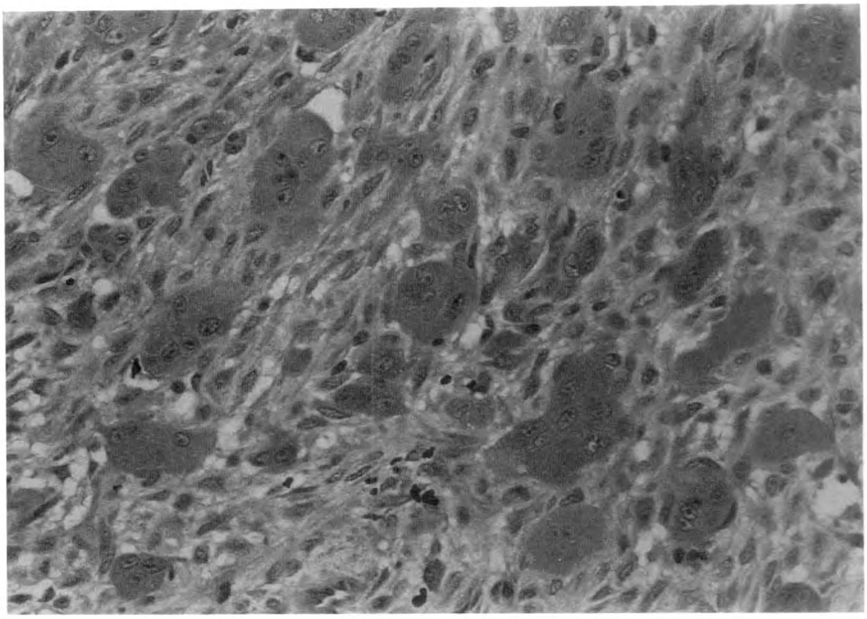


Fig 3. Brown tumor with spindled stroma and numerous multinucleate giant cells.

niques led to earlier diagnoses in frequently asymptomatic patients. Two studies from the early 1980s showed no bony changes in populations reviewed with primary hyperparathyroidism.[7,8] Today, the incidental finding of hypercalcemia in an asymptomatic patient is the most common method of diagnosis. Osteitis fibrosa cystica, bone cysts, and brown tumors have become extremely rare clinical entities. The modern physician must remain aware of these lesions and their association with primary hyperparathyroidism.

"Brown tumors" are somewhat inappropriately named, as these lesions are not truly neoplastic. They represent a reparative cellular process with foci of hemorrhage, fibrosis, and granulation tissue. Hemosiderin deposition imparts the characteristic brown color. Increased numbers of multinucleate giant cells, osteoblasts, and osteoclasts are also present. These lesions have histologic similarities to giant cell lesions.

Clinically, brown tumors are most frequently slow-growing lesions that can be locally destructive. Invasion into surrounding structures may cause a variety of symptoms. Patients often develop significant bone pain, and pathologic fractures may occur. Brown tumors of both the mandible and maxilla have been reported in the literature. An extensive review in the 1960s showed the mandible to be the most common site of involvement.[4] Location in the maxilla is rare.[4,5]

On radiographic evaluation, these tumors appear as well-defined, purely lytic lesions.[9,10] There is frequently cortical thinning and expansion. Generalized osteopenia may also be present. In the head and neck, computed tomography is exceptionally helpful in identifying the extent of these lesions. Attenuation values are typically in the range of blood and fibrous tissue. Bone scans may also aid in the diagnosis, with brown tumors being intensely active.

Central to the treatment of these lesions is correction of the hypercalcemia. With primary hyperparathyroidism, this most frequently requires parathyroidectomy. After treatment of the underlying metabolic disorder, brown tumors frequently become sclerotic and show regression. In our case, the brown tumor failed to regress in the 2 months after achieving normocalcemia. Surgical removal was curative and also provided material for pathologic examination. Where extensive cystic changes with attendant destruction have occurred, the extent of tissue damage may be too great to remodel with reversion of serum calcium levels to normal. In these cases, surgery may be required.

Skeletal disease resulting from primary hyperparathyroidism is now uncommon. Today, most patients are asymptomatic at the time of diagnosis. This case of a locally aggressive brown tumor reminds us that bone lesions can be manifestations of this disease.

REFERENCES

1. Herowitz M, Wishart JM, Need AG, Morris HA, Nordin BE. Primary hyperparathyroidism. Clin Geriatr Med 1994;10:757-72.

2. Ljunghall S, Hellman P, Rostad J, Akerstrom G. Primary hyperparathyroidism: epidemiology, diagnosis and clinical picture. World J Surg 1991;15:681-7.

3. Habener J, Arnold A, Potts JT Jr. Hyperparathyroidism. In: DeGroot LJ, ed. Endocrinology. 3rd ed. Philadelphia, Pa:

Saunders, 1995:1050-1.

4. Rosenberg EH, Guralnick WC. Hyperparathyroidism: a review of 220 proved cases with special emphasis on findings in the jaws. Oral Surg 1962;157(suppl 11):82-93.

5. Naimen J, Green WR, D'Heurle D. Brown tumor of the orbit associated with primary hyperparathyroidism. Am J Ophthalmol 1980;90:565-71.

6. Bassler T, Wong ET, Brynes RK. Osteitis fibrosa cystica simulating metastatic tumor. An almost forgotten relationship. Am J Clin Pathol 1993;100:697-700.

7. Mundy GR, Cove DH, Fisken R. Primary hyperparathyroidism: change in pattern of clinical presentation. Lancet 1980; i:1317-20.

8. Rao DS. Primary hyperparathyroidism: changing patterns in presentation and treatment decisions in the eighties. Henry Ford Hosp Med J 1985;33:194-7.

9. Hayes CW, Conway WF. Hyperparathyroidism. Radiol Clin North Am 1991;29:85-96.

10. Steinbach HL, Gordan GS, Eisenberg E, Crane JT, Silverman S, Goldman L. Primary hyperparathyroidism: a correlation of roentgen, clinical, and pathologic features. AJR Am J Roentgenol 1961;86:329-43.

≈

EAR SURGERY

The 34th Annual Postgraduate Course in Ear Surgery will be held April 5-10, 1999, in Nijmegen, the Netherlands. For information, contact Prof.dr. P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax +31 24 3540251; e-mail J.Cornelisse@kno.azn.nl.

Ann Otol Rhinol Laryngol 108:1999

CLINICOPATHOLOGICAL CONSULTATION

AIDS-RELATED PLASMABLASTIC LYMPHOMAS OF THE ORAL CAVITY AND JAWS: A DIAGNOSTIC DILEMMA

ANTONINO CARBONE, MD
AVIANO, ITALY

GIANLUCA GAIDANO, MD
NOVARA, ITALY

ANNUNZIATA GLOGHINI, PHD
AVIANO, ITALY

ALFIO FERLITO, MD
UDINE, ITALY

ALESSANDRA RINALDO, MD
PADUA, ITALY

HARALD STEIN, MD
BERLIN, GERMANY

Acquired immunodeficiency syndrome (AIDS)–related non-Hodgkin's lymphomas are highly pleomorphic in their clinical, pathological, and biological features. Recent investigations have led to the identification of a particular type of AIDS-related non-Hodgkin's lymphomas presenting in the oral cavity and jaws. This novel category of AIDS-related non-Hodgkin's lymphomas derives from B-cells and has been defined as plasmablastic lymphoma on the basis of its morphological and immunophenotypic features. Clinically, AIDS-related plasmablastic lymphoma is generally limited to the oral cavity at the time of diagnosis, although extension to distant sites frequently occurs at a later stage. Histologically, AIDS-related plasmablastic lymphoma is composed of a monomorphic and cohesive pattern of plasmablasts with basophilic cytoplasm. Phenotypically, AIDS-related plasmablastic lymphoma fails to express the most common B-cell–associated surface antigens, whereas it consistently expresses high levels of plasma cell–associated markers, including VS38c and CD138/syndecan-1. For the purpose of differential diagnosis, the morphological and immunophenotypic peculiarities of AIDS-related plasmablastic lymphoma clearly distinguish these lymphomas from other categories of AIDS-related non-Hodgkin's lymphomas, as well as from undifferentiated large cell carcinomas.

INTRODUCTION

The recent classification of acquired immunodeficiency syndrome (AIDS)–related lymphoproliferative disorders adopted by the International Agency for Research on Cancer/World Health Organization Working Group on AIDS and Tumours[1] has established that the spectrum of AIDS-related non-Hodgkin's lymphomas (AIDS-NHLs) includes systemic NHL, primary central nervous system lymphoma (PCNSL), and primary effusion lymphoma (PEL). Systemic AIDS-NHLs are heterogeneous and include 2 major pathologic categories, ie, small noncleaved cell lymphoma (SNCCL) and diffuse large B-cell lymphoma (DLCL). DLCL may be further distinguished into large noncleaved cell lymphoma (LNCCL) and large-cell immunoblastic lymphoma plasmacytoid (IBLP).[1,2] AIDS-PCNSL represents a relatively uniform group and tends, in almost all cases, to display histologic features consistent with IBLP and LNCCL categories.[3] AIDS-PEL is consistently associated with Kaposi's sarcoma–associated herpesvirus and morphologically bridges immunoblastic and anaplastic features.[1,4,5]

Despite this diversity, however, all AIDS-NHLs share a number of similarities. They all derive from B-cells, they are characterized by widespread disease at presentation, and they show a predilection for extranodal sites. In particular, a significant proportion of AIDS-NHLs may involve the head and neck. As for AIDS-NHLs, in general, human immunodeficiency virus (HIV)–infected patients with head and neck NHLs have severe immunodeficiency, extranodal disease, aggressive histologic findings, and a poor response to treatment.[6]

AIDS-NHL may occur anywhere in the head and neck area. The tumor has been observed in a variety of sites, including the gingiva, palate, tongue, tonsil, nasopharynx, orbit, parotid, maxillary sinus, soft tissue, and hypopharynx.[6-13] Most AIDS-NHLs of the head and neck are morphologically similar to other lymph nodal or extranodal systemic AIDS-NHLs and express B-cell markers.

AIDS-RELATED PLASMABLASTIC LYMPHOMAS OF THE ORAL CAVITY

Definition. A particular type of lymphoma has re-

From the Division of Pathology, National Cancer Institute, Istituto di Ricovero e Cura a Carattere Scientifico, Aviano (Carbone, Gloghini), the Division of Internal Medicine, Department of Medical Sciences, University of Turin at Novara, Novara (Gaidano), the Department of Otolaryngology–Head and Neck Surgery, University of Udine, Udine (Ferlito), and the Department of Otolaryngology, University of Padua, Padua (Rinaldo), Italy, and the Institute of Pathology, Klinikum Benjamin Franklin, Free University of Berlin, Berlin, Germany (Stein). Supported in part by the Ministero della Sanità, Istituto Superiore di Sanità, AIDS Projects 1996 and 1997, Rome, Italy, and by the Piera Pietro e Giovanni Ferrero Foundation, Alba, Italy.

CORRESPONDENCE — Alfio Ferlito, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Udine, Policlinico Città di Udine, Viale Venezia 410, 33100 Udine, Italy.

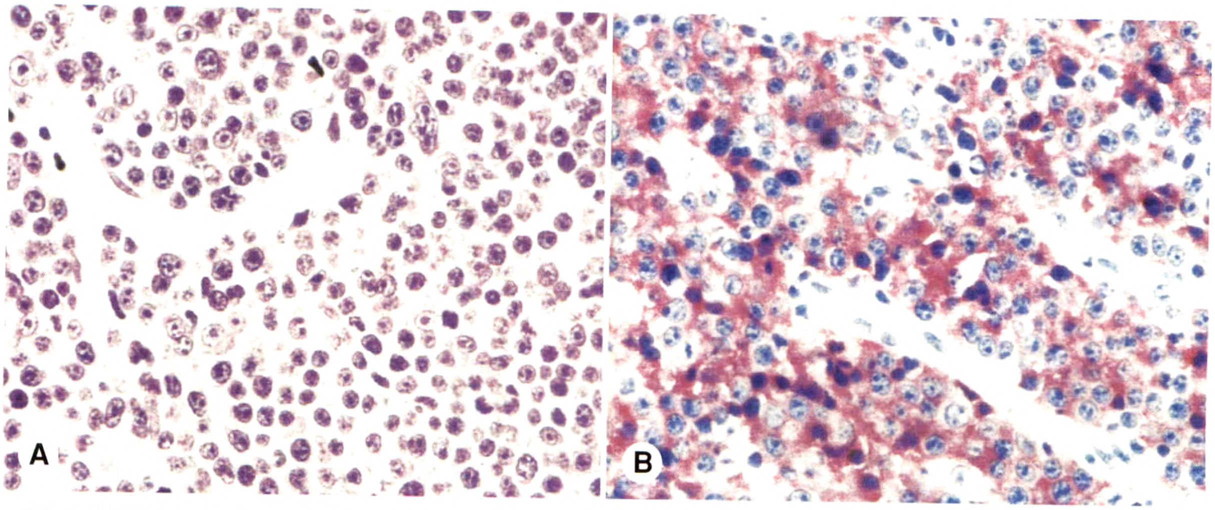


Fig 1. AIDS-related plasmablastic lymphoma of oral cavity. A) Morphology (H & E, original ×250). B) All neoplastic cells are strongly labeled by anti-CD138/B-B4 antibody (alkaline phosphatase–anti–alkaline phosphatase method, hematoxylin counterstain, original ×250).

cently been identified as a specific entity among AIDS-DLCLs involving the oral cavity.[14] These lymphomas have been designated as "plasmablastic lymphomas" (PBLs) in accordance with their plasmablastic morphology and immunohistologic features.[14] The real incidence of this new entity is still unknown. In a consecutive series of 191 AIDS-NHLs observed at one institution between 1984 and 1997, AIDS-PBL accounted for 2.6% of cases.[15]

Clinical Features. From a clinical standpoint, AIDS-PBL is associated with a distinctive clinical feature that greatly contributes to its diagnosis, ie, origin in the oral cavity. All the reported AIDS-PBLs were extranodal, the tumors were localized in the mucosa of the oral cavity, and they often involved the gingiva. In several instances, the bulk of the tumor infiltrated the adjacent bone, as assessed by radiographic analysis[14] (also unpublished observations, A. Carbone, 1998). In most patients, the tumor was limited to the oral cavity at the time of diagnosis, but the extension of AIDS-PBL to distant sites (abdomen, retroperitoneum) and other organs (bones and ovary) could be identified shortly after the diagnosis. None of the patients exhibited a serum monoclonal immunoglobulin (Ig). All AIDS-PBLs proved very aggressive clinically, and the prognosis was poor (survival 1 to 16 months) despite chemotherapy[14] (also unpublished observations, A. Carbone, 1998) with or without combined radiotherapy.[14] Only 3 patients with AIDS-PBL limited to the oral cavity responded well to radiotherapy alone.[14]

Histologic Features. The neoplastic infiltrate usually effaces the normal architecture of the mucosa. Extension to the submucosal compartment, as well as to the mucosal surfaces, with ulceration, also occurs. The histologic appearance of AIDS-PBL is relatively monomorphic. AIDS-PBL displays a diffuse and cohesive growth pattern with large neoplastic cells exhibiting a squared-off appearance. These cells have a centrally or eccentrically placed nucleus with a single prominent nucleolus or several nucleoli[14,15] (Fig 1A). Russell bodies and Dutcher bodies are not present. The cytoplasm is abundant and appears deeply basophilic after Giemsa staining. Apoptotic figures are numerous, and single cell necrosis is common. Only a few, small reactive lymphocytes, of both B- and T-cell origin, are found to be admixed with the neoplastic population.

Immunophenotype. According to their morphologic features, AIDS-PBL tumor cells display a blastic cell morphology with plasma cell differentiation. This is consistent with their unusual immunophenotype, which is characterized by a weak or absent expression of the most commonly used lymphoid markers. A monotypic light chain expression can be demonstrated in about one third of cases. Conversely, AIDS-PBL displays strong immunostaining with the new plasma cell reacting antibodies VS38c and CD138/B-B4[14,15] (Fig 1B). Overall, the AIDS-PBL immunophenotype ($CD20^-$, $CD45^{-/+}$, $CD79a^{-/+}$, EMA^+, $VS38c^+$, $CD138/B\text{-}B4^+$) is consistent with a marked plasma cell differentiation of the tumor clone.

Differential Diagnosis. Awareness of these morphologic and immunohistologic features can greatly contribute to the diagnostic differentiation between AIDS-PBLs and non-lymphoid malignancies. In fact, the observation that CD20, CD79a, and CD45 expression is lacking in an undifferentiated large cell tumor of the oral cavity in HIV-infected people could erroneously lead to the exclusion of lymphoma from

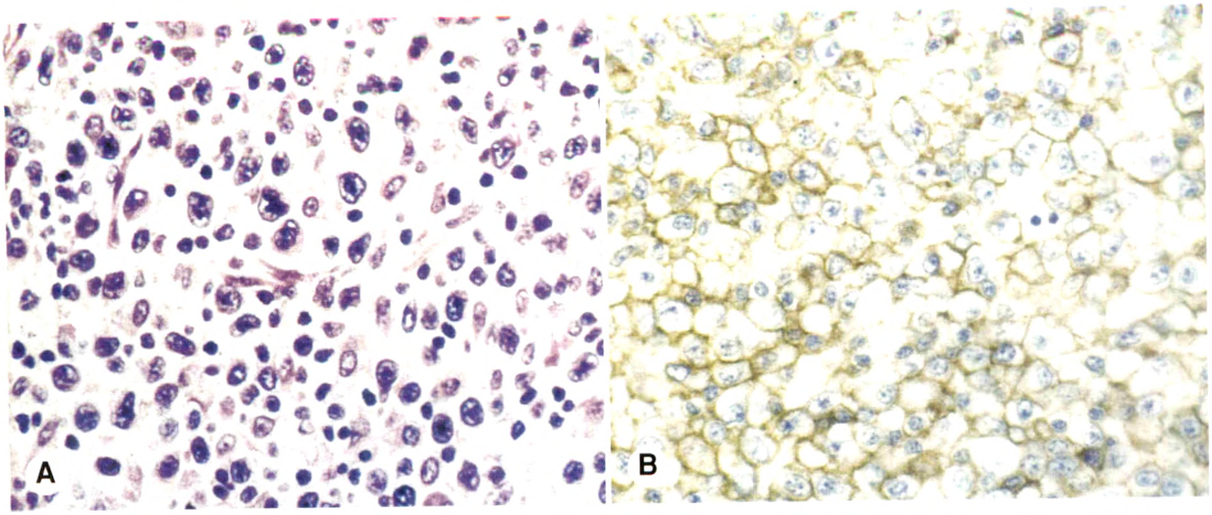


Fig 2. Systemic AIDS-related large-cell lymphoma of immunoblastic plasmacytoid subtype. A) Morphology (H & E, original ×250). B) High number of tumor cells show membranous staining with CD45 antibody (avidin biotin complex–peroxidase method, hematoxylin counterstain, original ×250).

differential diagnosis. In this respect, knowledge of the existence of AIDS-PBL makes the application of plasma cell–reacting antibodies and antibodies to Ig chains mandatory in order to avoid confusion with undifferentiated carcinomas or sarcomas. AIDS-PBL may also be confused with a DLCL of the IBLP type (Fig 2) and with plasmacytomas (Fig 3). The distinction of AIDS-PBL from AIDS-IBLP can be made on immunophenotypic grounds because of the strong expression of CD20 and CD45 by IBLP tumor cells (Fig 2B). On the other hand, morphologic details can distinguish AIDS-PBL from plasmacytoma. In fact, AIDS-PBLs are entirely composed of blastic-appearing cells and do not contain the pro-plasma cells and mature plasma cells typical of plasmacytomas (Fig 3A). Major difficulties may occur when a solitary plasmacytoma displays anaplastic features (anaplastic plasmacytoma), because they have mostly blastoid-appearing cells with only a few clearly differentiated plasma cells. Among extranodal AIDS-NHLs with plasma cell differentiation,[15] AIDS-PBLs share several features with AIDS-NHL cases presenting "intermediate" features between SNCCL and IBLP[16] (also termed Burkitt-like lymphoma[2]). The "intermediate" lymphomas display a cytoplasmic positivity for CD20 and CD45 in a variable proportion of the tumor cells. The VS38c, CD138/B-B4, and epithelial membrane antigen staining is also seen in the "intermediate" lymphoma cases, but it is usually confined to a minority of cells. Staining with CD79a and CD43 monoclonal antibodies is found in a fraction of "intermediate" lymphomas. Thus, AIDS-PBL may be differentiated on the basis of the infrequent or absent expression of CD45 (positive in "intermediate" lymphoma) and constant reaction to the new plasma cell–reacting antibodies VS38c

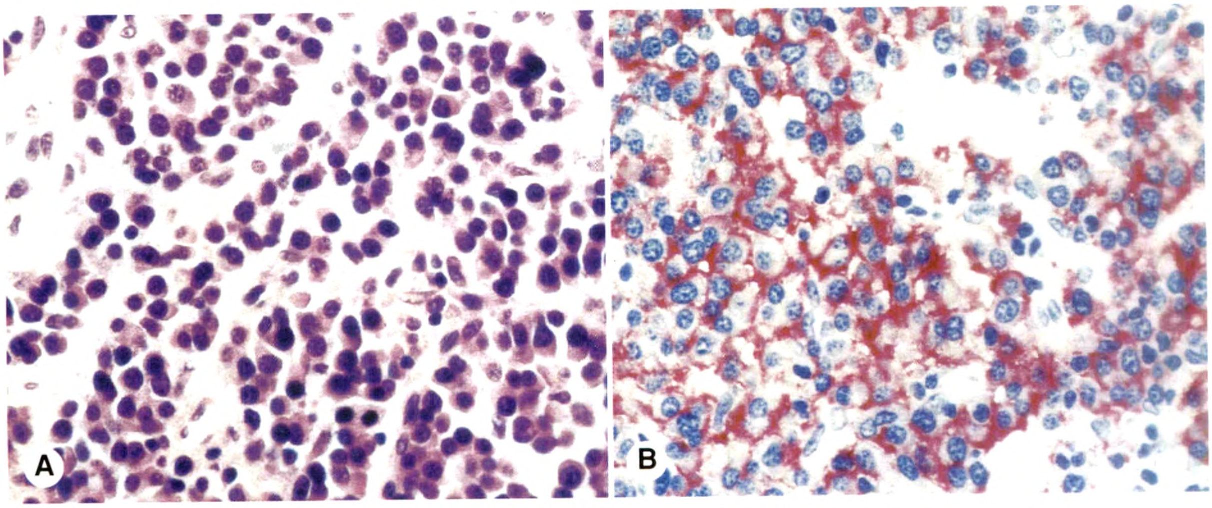


Fig 3. Extramedullary plasmacytoma. A) Morphology (H & E, original ×250). B) All neoplastic cells show strong membrane staining with anti-CD138/B-B4 antibody (alkaline phosphatase–anti–alkaline phosphatase method, hematoxylin counterstain, original ×250).

and CD138/B-B4.

Histogenesis. Recent evidence from our group has determined that the expression pattern of 2 biologic markers, namely, CD138/syndecan-1 and BCL-6, identifies distinct histogenetic pathways among AIDS-NHLs.[17] CD138/syndecan-1 belongs to the syndecan family of proteoglycans, whereas the BCL-6 protein is the gene product of a zinc finger transcription factor frequently involved in the pathogenesis of AIDS-NHL and NHL of the immunocompetent host.[18,19] Whereas CD138/syndecan-1 represents a marker of preterminal and terminal B-cell differentiation, expression of BCL-6 selectively associates with the germinal center (GC) stage of B-cell maturation.[20,21] Expressions of BCL-6 and CD138/syndecan-1 are mutually exclusive in the B-cell lineage.[17] On these bases, AIDS-NHLs expressing the BCL-6^+/syndecan-1^- phenotype, ie, AIDS-SNCCL and AIDS-LNCCL, are thought to derive from GC-related cells.[17] Conversely, AIDS-NHLs expressing the BCL-6^-/syndecan-1^+ phenotype, ie, AIDS-IBLP and AIDS-PEL, would derive from post-GC, preterminal B-cells.[17] AIDS-PBLs of the oral cavity consistently display the BCL-6^-/syndecan-1^+ phenotype, thus suggesting that these lymphomas are histogenetically related to preterminally differentiated B-cells.

CONCLUSIONS

At present, AIDS-PBL is not formally recognized as an individual entity in AIDS-NHL classification schemes. Yet, the particular clinical, morphologic, and immunophenotypic features of AIDS-PBL make it essential for it be singled out as an individual clinicopathological category. Several tumor entities, including nonlymphoid large cell tumors and other extranodal AIDS-related lymphoproliferations with plasma cell differentiation (AIDS-IBLP, plasmacytomas, and "intermediate" AIDS-NHL), should be considered in the differential diagnosis of AIDS-PBL. However, careful analysis of the morphology and/or phenotype enables the distinction of AIDS-PBL from other neoplasms.

An emerging notion in the field of AIDS-NHL is that the pathologic and biologic features of these disorders appear to correlate with clinical behavior and prognosis — hence, the need to establish detailed biologic diagnostic criteria for each AIDS-NHL category. In this respect, research efforts should be directed at defining the precise biologic and pathogenetic features of AIDS-PBL and characterizing the relationship of these tumors to other extranodal AIDS-NHLs with plasma cell differentiation.

REFERENCES

1. International Agency for Research on Cancer. Human immunodeficiency viruses and human T-cell lymphotropic viruses. In: IARC monographs on the evaluation of carcinogenic risks to humans. Vol 67. Lyon, France: World Health Organization International Agency for Research on Cancer, 1996.

2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84: 1361-92.

3. Camilleri-Broët S, Davi F, Feuillard J, et al. AIDS-related primary brain lymphomas: histopathologic and immunohistochemical study of 51 cases. Hum Pathol 1997;28:367-74.

4. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity–based lymphomas. N Engl J Med 1995;332:1186-91.

5. Carbone A, Gloghini A, Vaccher E, et al. Kaposi's sarcoma–associated herpesvirus DNA sequences in AIDS-related and AIDS-unrelated lymphomatous effusions. Br J Haematol 1996; 94:533-43.

6. Carbone A, Vaccher E, Barzan L, et al. Head and neck lymphomas associated with human immunodeficiency virus infection. Arch Otolaryngol Head Neck Surg 1995;121:210-8.

7. Brahim JS, Katz RW, Roberts MW. Non-Hodgkin's lymphoma of the hard palate mucosa and buccal gingiva associated with AIDS. J Oral Maxillofac Surg 1988;46:328-30.

8. Green TL, Eversole LR. Oral lymphomas in HIV-infected patients: association with Epstein-Barr virus DNA. Oral Surg Oral Med Oral Pathol 1989;67:437-42.

9. Kaugars GE, Burns JC. Non-Hodgkin's lymphoma of the oral cavity associated with AIDS. Oral Surg Oral Med Oral Pathol 1989;67:433-6.

10. Leess FR, Kessler DJ, Mickel RA. Non-Hodgkin's lymphoma of the head and neck in patients with AIDS. Arch Otolaryngol Head Neck Surg 1987;113:1104-6.

11. Shapiro AL, Shechtman FG, Guida RA, Kimmelman CP. Head and neck lymphoma in patients with the acquired immune deficiency syndrome. Otolaryngol Head Neck Surg 1992; 106:258-60.

12. Groot RH, Van Merkesteyn JP, Bras J. Oral manifestations of non-Hodgkin's lymphoma in HIV-infected patients. Int J Oral Maxillofac Surg 1990;19:194-6.

13. Epstein JB, Silverman S Jr. Head and neck malignancies associated with HIV infection. Oral Surg Oral Med Oral Pathol 1992;73:193-200.

14. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413-20.

15. Carbone A, Gloghini G, Canzonieri V, Tirelli U, Gaidano G. AIDS-related extranodal non-Hodgkin's lymphomas with plasma cell differentiation. Blood 1997;90:1337-8.

16. Carbone A, Gloghini A, Gaidano G, et al. AIDS-related Burkitt's lymphoma: morphologic and immunophenotypic study of biopsy specimens. Am J Clin Pathol 1995;103:561-7.

17. Carbone A, Gaidano G, Gloghini A, et al. Differential expression of BCL-6, CD138/syndecan-1 and EBV-encoded la-

tent membrane protein-1 identifies distinct histogenetic subsets of AIDS-related non-Hodgkin's lymphomas. Blood 1998; 91:747-55.

18. Bernfield M, Kokenyesi R, Kato M, Spring J, Gallo RL, Lose EJ. Biology of the syndecans: a family of transmembrane heparan sulfate proteoglycans. Annu Rev Cell Biol 1992;8:365-93.

19. Ye BH, Lista F, Lo Coco F, Knowles DM, Chaganti RSK, Dalla-Favera R. Alterations of BCL-6, a novel zinc-finger gene, in diffuse large cell lymphoma. Science 1993;262:747-50.

20. Cattoretti G, Chang CC, Cechova K, et al. BCL-6 protein is expressed in germinal-center B cells. Blood 1995;86:45-53.

21. Wijdenes J, Voojis WC, Clément C, et al. A plasmocyte selective monoclonal antibody (B-B4) recognizes syndecan-1. Br J Haematol 1996;94:318-23.

≈

INTERNATIONAL MEETING ON OTOLOGY

The International Meeting on Otology of the Jean Causse Ear Clinic will be held June 5, 1999, in Béziers, France. For more information, please contact Robert Vincent, MD, Jean Causse Ear Clinic, Traverse de Béziers, 34440 Colombiers, France; telephone (33) 4-67-35-62-62; fax (33) 4-67-35-62-00.

BOOK REVIEW

American Sign Language: Shattering the Myth

Tom Bertling, editor. Soft cover, 112 pages, 1998. Kodiak Media Group, Wilsonville, Ore, $19.95.

Purpose: To show that American Sign Language (ASL) in respect to attainable language is based on false premises and is the product of fallacious reasoning.

Contents: Two essays by past professors from Gallaudet University and 4 additional contributions, the last being that of a book review and discussion, all wishing to give a background on the present-day method of educating the deaf, especially at Gallaudet and state institutions.

Attributes: If one wanted to know first-hand the pitfalls of the Bolshevik Revolution, Karl Marx would have been a good source. The professionals conveying the critical analysis of ASL in this essay are all proponents of sign language of English word order and not advocates of oral education. Hence, they seem to favor speech with signs. Their arguments against ASL are that there is no true method to language development for all deaf children; that most children from state institutions do not read past third-grade levels and cannot read a newspaper or fill out a job application; that 80% of graduates of state deaf schools are on Social Security disability and receive Supplemental Security Income; and that above all, the ASL of today is a language of the deaf prior to learning English word order — nothing more than "street signs."

Limitations: It is a book of essays, or, one may say, a "book of opinion."

Applicability: These accounts are well worth reading. Given the horrific information, the group of essays is a grim indictment of official fanaticism. All physicians, especially otolaryngologists who deal with congenital profound sensorineural hearing loss, should find this summary of the current state of knowledge useful.

DENNIS G. PAPPAS, MD
Birmingham, Alabama

Ann Otol Rhinol Laryngol 108:1999

HISTOPATHOLOGY OF CONGENITAL SUBGLOTTIC STENOSIS

LAUREN D. HOLINGER, MD

CHICAGO, ILLINOIS

A precise delineation of each laryngeal abnormality is critical to planning rational therapy. Since congenital cricoid cartilage anomalies are easily overlooked, a systematic approach to their identification is as important as a clear concept of their classification. The purpose of this communication is to present the pathologic findings and classification of congenital cricoid cartilage deformities and to summarize updated information derived by the whole organ macrosection technique. The classification of congenital subglottic stenosis is based on study of the English-language literature and the collection in the Laryngeal Development Laboratory at The Children's Memorial Hospital in Chicago. Twenty-nine specimens with congenital cricoid abnormalities have been identified. Fourteen have an elliptical cricoid cartilage; 12, a laryngeal cleft; 5, a flattened shape; 1, a large anterior lamina; and 3, generalized thickening. Some specimens have more than 1 anomaly. Eight cases of fragmented or distorted cricoid cartilages are thought to be acquired lesions. An anterior submucous cricoid cleft has been identified and is presented for the first time.

KEY WORDS — cleft larynx, congenital laryngeal anomalies, congenital subglottic stenosis, cricoid cartilage deformity, laryngotracheoesophageal cleft, occult laryngeal cleft, submucous laryngeal cleft.

A study of the material from the laboratory and the English-language literature has led to a classification of cartilaginous cricoid cartilage abnormalities that provides a framework for the conceptualization of normal laryngeal anatomy and of congenital and acquired subglottic stenosis (Table 1). Why is an understanding of the various cricoid anomalies important to the clinical otolaryngologist–head and neck surgeon? There are 2 specific reasons. First, rational therapy of laryngotracheal stenosis cannot be planned without defining the precise extent and nature of each lesion. For example, cartilaginous stenoses are not responsive to dilation or laser vaporization, but these modalities can often be used to treat soft tissue subglottic stenosis. Second, congenital subglottic stenosis can be a contributing factor in the formation of acquired laryngeal stenosis; an abnormally narrowed larynx has a greater chance of being traumatized by an endotracheal tube of age-appropriate size than does the normal airway.

TABLE 1. CLASSIFICATION OF SUBGLOTTIC STENOSIS

- Cartilaginous stenosis (usually congenital)
  - Cricoid cartilage deformity
    - Normal shape, small size
    - Abnormal shape
      - Elliptical shape
      - Flattened shape
      - Laryngeal clefts
      - Thickened cricoid
      - Acquired lesions
  - Trapped first tracheal ring
- Soft tissue stenosis (usually acquired)
  - Submucosal mucous gland hyperplasia
  - Ductal cysts
  - Submucosal fibrosis
  - Granulation tissue

The horizontal serial section study of the larynx by Tucker et al[1] contributes to our understanding that the upper posterior lamina of the normal cricoid cartilage is a "V" configuration (Fig 1A,B) rather than a gently curved arc. Sections through the midcricoid level reveal the lumen to be elliptical in shape (Fig 1B). Only at its inferior portion does the cricoid cartilage assume the shape of a smooth, round ring (Fig 1C). Specimens from the Laryngeal Development Laboratory, The Children's Memorial Hospital, Chicago, Illinois, have a variety of specific cricoid cartilage anomalies that had been diagnosed clinically merely as subglottic stenosis. Careful inspection and critical thinking permit a more precise identification of each specific laryngeal anomaly.

The clinical diagnosis of congenital subglottic stenosis encompasses a variety of conditions that narrow the subglottic airway. P. H. Holinger et al[2] described an abnormally shaped cricoid cartilage causing subglottic stenosis as early as 1954. McMillan and Duvall[3] reported 2 additional cases of congenital stenosis, the first circumferential and the second limited more to the posterior lamina of the cricoid

---

From the Division of Pediatric Otolaryngology, The Children's Memorial Hospital, and the Department of Otolaryngology–Head and Neck Surgery, Northwestern University Medical School, Chicago, Illinois. The Laryngeal Development Laboratory at The Children's Memorial Hospital is supported by the Lillian Shedd Wells Foundation and the Children's Surgical Foundation.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 11-12, 1998.

CORRESPONDENCE — Lauren D. Holinger, MD, Division of Pediatric Otolaryngology, The Children's Memorial Hospital, Box 25, 2300 Children's Plaza, Chicago, IL 60614.

cartilage. Other authors also have reported cartilaginous abnormalities of the cricoid causing subglottic stenosis.[4] Fearon and Cotton[5] categorized 3 different forms of subglottic stenosis based on the cricoid cartilage in 1972. Current thinking classifies congenital subglottic stenosis according to the morphology of the cricoid cartilage (Table 2).

MATERIALS AND METHODS

The whole organ serial section technique originally used to study the spread of carcinoma within the larynx has also been applied to study the anatomy and development of the human embryonic, fetal, infant, and adult larynx. In 1975, the Laryngeal Development Laboratory was established at The Children's Memorial Hospital in Chicago by Gabriel F. Tucker, Jr, MD, for the evaluation of normal and abnormal larynges with congenital and acquired lesions.

Larynges are acquired at postmortem examination, when removal is carried out in a conventional manner (Rokitansky). Most specimens include the entire hyoid bone superiorly, 2 or more tracheal rings inferiorly, and the hypopharyngeal mucosa posteriorly. The block of tissue obtained is kept intact, unsplit, and fixed in 10% formalin. After decalcification and fixation, it is imbedded in Parlodion (pyroxylin), then serially sectioned at 28 μm in the horizontal plane from top to bottom. Every 20th section is mounted and stained with hematoxylin and eosin. The remaining sections are numbered and stored in 80% alcohol for later staining, if necessary.

RESULTS

To date, 129 specimens have been obtained at autopsy. One hundred twenty-two have been sectioned and examined. Twenty-nine have been determined to have congenital cricoid cartilage abnormalities.

NORMAL SHAPE, SMALL SIZE

The small cricoid is difficult to identify if the general shape of the cricoid and other laryngeal structures are otherwise normal. A cricoid diameter of less than 3.5 mm in the newborn is indicative of subglottic stenosis.[6] Careful and objective measurement during endoscopy and postmortem examination is required.

ELLIPTICAL SHAPE

The elliptical cricoid cartilage is the most common congenital anomaly in the collection. Most of these specimens have other anomalies as well. In our clinical experience, it is the most frequently diagnosed abnormal cricoid shape that causes congenital subglottic stenosis.

The elliptical cricoid cartilage was first described in 1979 by Tucker et al.[7] While the lumen in the midlevel of the cricoid cartilage is normally elliptical, at the inferior margin the transverse and anteroposterior diameters of the normal larynx should be equal as a result of the characteristic ring configuration of the cricoid at this level. However, as seen in Fig 2C, the transverse diameter of the elliptical cricoid at the lower level is considerably less than the anteroposterior diameter. This results in a loss of the cross-sectional area, which may cause respiratory distress, as well as predisposing the larynx to injury from endotracheal tube intubation. The elliptical cricoid cartilage is often found in association with other congenital laryngeal anomalies such as the posterior laryngeal cleft (PLC).

FLATTENED SHAPE

The flattened cricoid, in contradistinction to the elliptical cricoid, has a transverse diameter greater than the anteroposterior diameter. Figure 3 shows an example of this anomaly. This specimen also has hypertrophy of the submucosal mucous glands, probably an acquired condition. The flattened shape may also be associated with a trapped first tracheal ring.[7] In the trapped first tracheal ring anomaly, the first tracheal ring rides up inside the cricoid cartilage, where it can reduce the size of the lumen, contributing to congenital subglottic stenosis.

THICKENED CRICOID

A generalized thickened cricoid has been observed both clinically (at the time of laryngotracheal reconstruction) and in the laboratory. It may be difficult to know with certainty whether such lesions are congenital or acquired. Only in the absence of any history of tracheal intubation or infection can it be assumed that such abnormalities are purely congenital.

A large anterior lamina has been found in association with a trapped first tracheal ring (Fig 4). The

TABLE 2. CRICOID CARTILAGE DEFORMITIES

- Normal shape, small size
- Abnormal shape
  - Elliptical shape
  - Flattened shape
  - Thickened cricoid
    - Large anterior or posterior lamina
    - Generalized thickening
  - Laryngeal clefts
    - Submucous (anterior or posterior)
    - Posterior laryngeal cleft, types I to III
  - Acquired lesions
    - Fragmented, distorted cricoid
    - Cricoid ossification

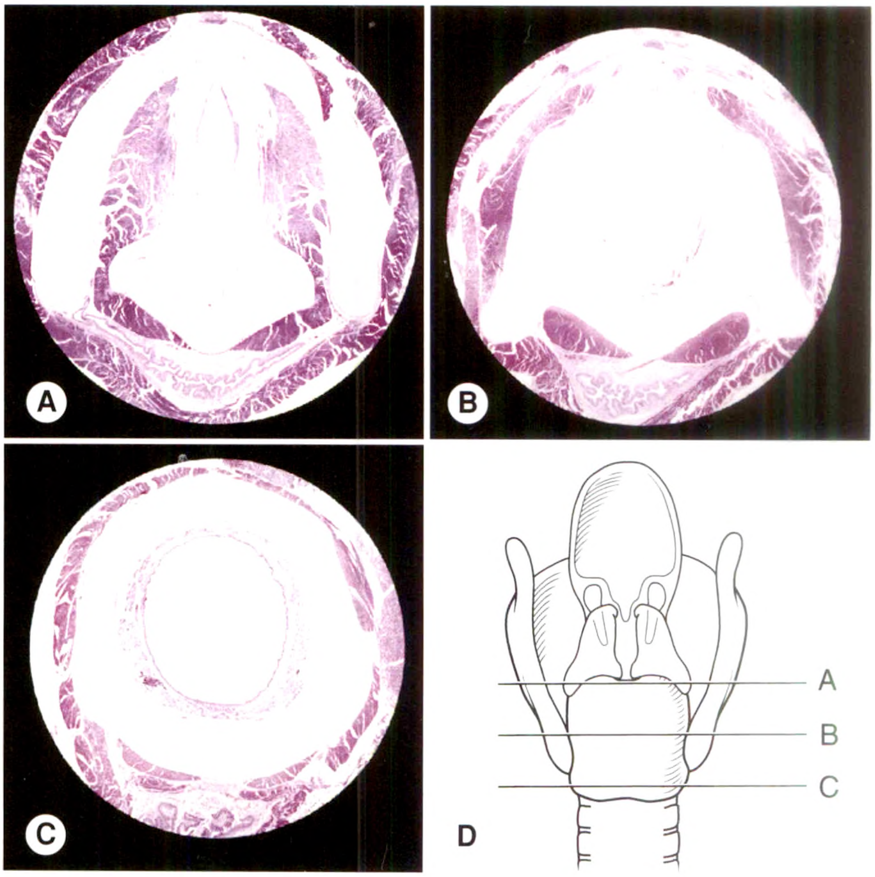


Fig 1. Normal anatomy. Horizontal sections through larynx of 18-month-old child. A) V-shape of superior part of cricoid cartilage is apparent posteriorly at level of glottis. B) At midcricoid level, V-shape of posterior cricoid cartilage persists. Lumen is elliptical. Cricoid cartilage ring is not complete anteriorly at this level. C) At inferior level of cricoid, lumen and cartilage are smooth, round shape. Amount of soft tissue within cricoid ring is probably normal or slightly increased in this larynx. D) Level of each horizontal section is indicated on this illustration of posterior aspect of larynx.

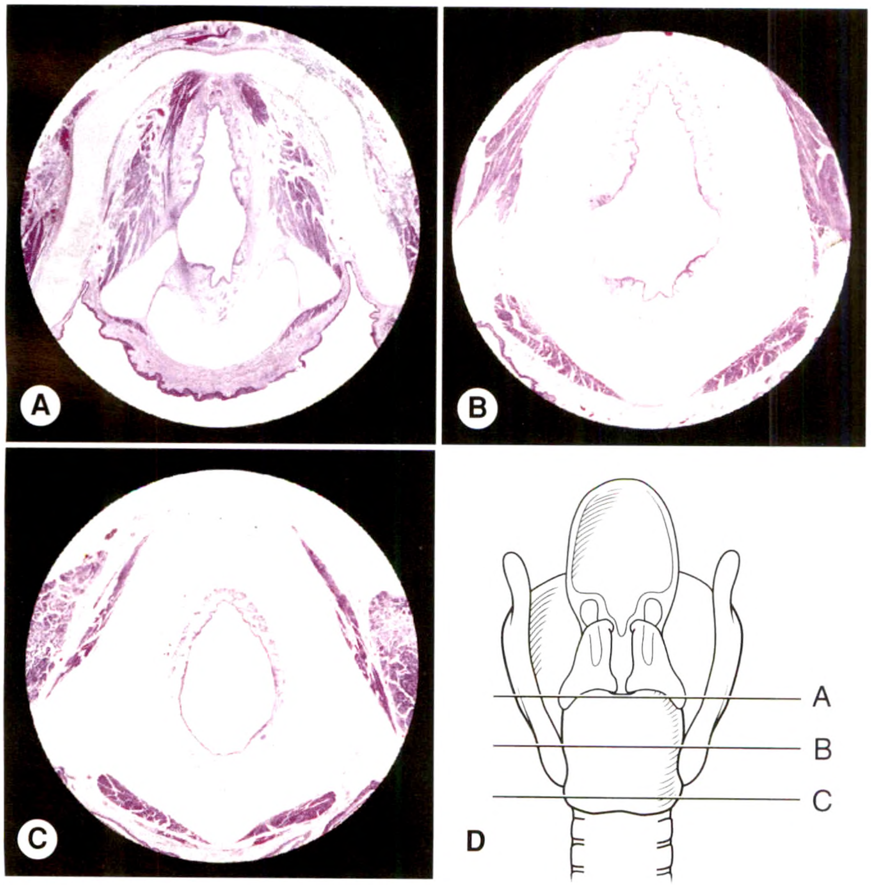


Fig 2. Elliptical cricoid cartilage. A) Superior, glottic level. B) Midcricoid level. Soft tissue changes (bilateral ulcerations) are due to endotracheal tube injury. C) Inferior cricoid level. Transverse diameter at inferior level is considerably less than anteroposterior diameter. In normal cricoid cartilage configuration, these should be equal at this inferior level. D) Reconstruction indicating level of each section from posterior aspect.

cricoid cartilage is thickened anteriorly; in this specimen the first tracheal ring is located abnormally cephalad. The endoscopic appearance is that of a horizontal curvilinear ridge or "step-off" anteriorly at the junction between the cricoid and the first tracheal ring. This "trapped first tracheal ring" within the cricoid lumen may cause a significant loss of anterior-posterior diameter.

LARYNGEAL CLEFTS

Posterior laryngeal clefts and laryngotracheoesophageal clefts (LTECs) were first recognized and described by Richter in 1792. The PLC is characterized by an absence of fusion of the posterior cricoid lamina that effects an abnormal communication between the larynx and hypopharynx. In the more extensive form of LTEC, absence of all or part of the tracheoesophageal septum effects an abnormal communication between the trachea and esophagus as well.

The condition varies in anatomic extent and clinical severity. In its mildest form, the submucous (occult) PLC, the only abnormality is a defect in the posterior lamina of the cricoid cartilage; the soft tissue is intact. The PLC type I is characterized by absence of the interarytenoid muscle above the superior margin of the cricoid cartilage. Affected patients may survive into adulthood with nothing more serious than hoarseness and recurrent respiratory tract infections. In more severe forms (LTEC types III and IV), in which the cricoid and posterior tracheal wall are cleft, death due to severe aspiration pneumonia and respiratory failure may be inevitable.

Twelve cases of laryngeal cleft anomalies have been identified to date. Nine have a submucous ("occult") laryngeal cleft. The collection also contains 1 LTEC type II (partial cricoid cleft), and 2 LTEC type III (total cricoid cleft) specimens (Table 3).

SUBMUCOUS ("OCCULT") LARYNGEAL CLEFT

The submucous laryngeal cleft consists of a midline submucous cartilage defect (cleft) with intact soft tissue including mucosa and interarytenoid muscle. When viewed on horizontal cross section, the edges of the cleft cartilage are rounded, smooth, and covered with perichondrium.

In the submucous laryngeal cleft, the cricoid may be cleft anteriorly or posteriorly. The posterior submucous laryngeal cleft was first reported by Tucker and Maddalozzo.[8] Those reported herein include 8 posterior submucous clefts previously reported.[9] A case of anterior submucous laryngeal cleft is described and added to the series.

Posterior. Sections taken superior to the posterior cartilage defect demonstrate a distorted cartilage (Fig 5). Sections inferior to the cleft demonstrate an intact cartilaginous ring. Deformities of the cricoid cartilage associated with submucous laryngeal cleft include the elliptical cricoid.

All except 1 case of submucous laryngeal cleft had associated subglottic stenosis; 1 also had tracheal stenosis. Six of the 8 cases of posterior submucous laryngeal cleft were found in preterm infants who had an average gestational age of 26.2 weeks and an average birth weight of 783 g. Two infants were term. All 8 had been intubated at birth for treatment of respiratory distress due to bronchopulmonary dysplasia, upper airway obstruction, and apneic episodes. Most had congenital cardiovascular anomalies. Of the cases reported herein, the diagnosis of submucous cleft was never made during life; they were identified only at postmortem pathologic examination.

Anterior. A case of anterior submucous laryngeal cleft has been identified. No description of a midline anterior cricoid cleft has heretofore been reported in the English-language literature. The full-term male infant died at age 3 days. He was intubated shortly after birth and ultimately died a cardiorespiratory death. He had multiple congenital anomalies, including micrognathia, cleft upper lip, hypertrophic thumbs, hypospadias, bilateral undescended testes, bilateral club feet, dysplastic right kidney, bilateral hydroureter, and multiple congenital cardiovascular anomalies. He had a normal 46,XY male karyotype.

Examination of the cricoid cartilage shows incomplete fusion of the cricoid anteriorly (anterior submucous laryngeal cleft; Fig 6). Subglottic stenosis is present; the transverse diameter is approximately 50% smaller than normal. The anteroposterior diameter is also somewhat compromised; the lumen has an elliptical shape. The thyroid cartilage is intact; no ventral cleft of the thyroid cartilage is present. Tracheal stenosis is present as well.

TABLE 3. LARYNGEAL CLEFTS

Type of Cleft		*No. of Clefts*
Submuccus (occult) cleft		9
Posterior	8	
Anterior		
Cricoid cartilage	1	
Thyroid cartilage	0	
Posterior laryngeal cleft, type I (PLC I, LTEC I)		0
Posterior laryngeal cleft, type II (PLC II, LTEC II)		1
Laryngotracheoesophageal cleft, type III (LTEC III)		2
Laryngotracheoesophageal cleft, type IV (LTEC IV)		0
Total clefts		12

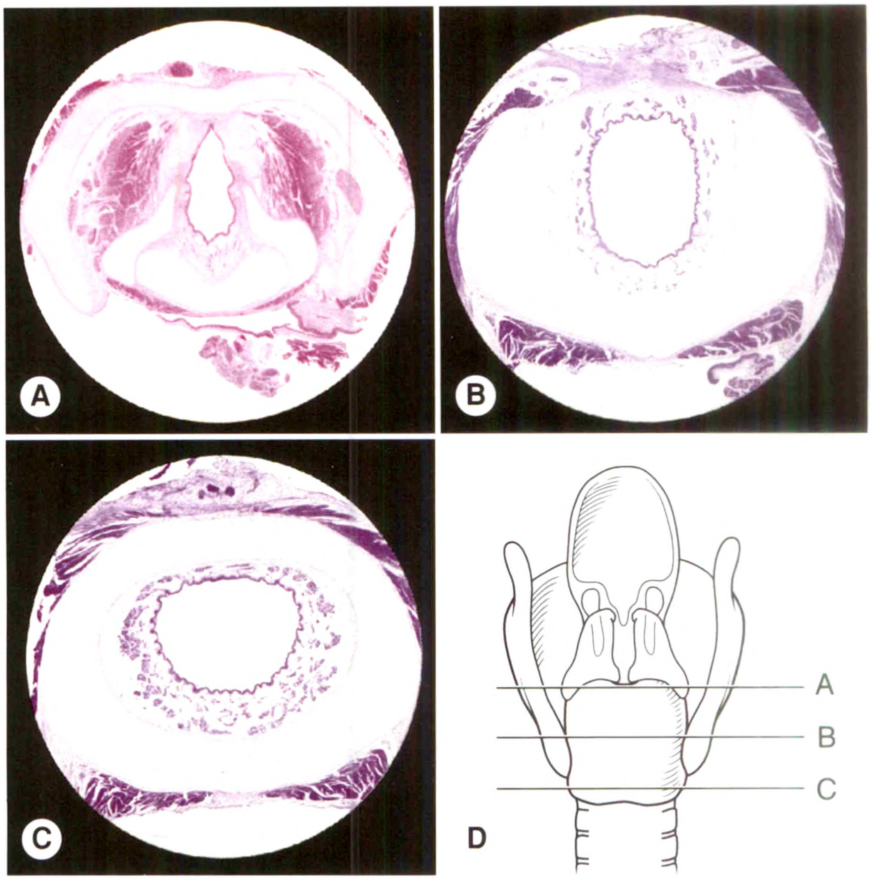


Fig 3. Flattened cricoid cartilage. This specimen also has associated hyperplasia of submucosal mucous glands. A) Superior, glottic level. B) Midcricoid level. C) Inferior cricoid level. Transverse diameter is normal, but anteroposterior dimension is compromised at inferior level. D) Reconstruction from posterior aspect.

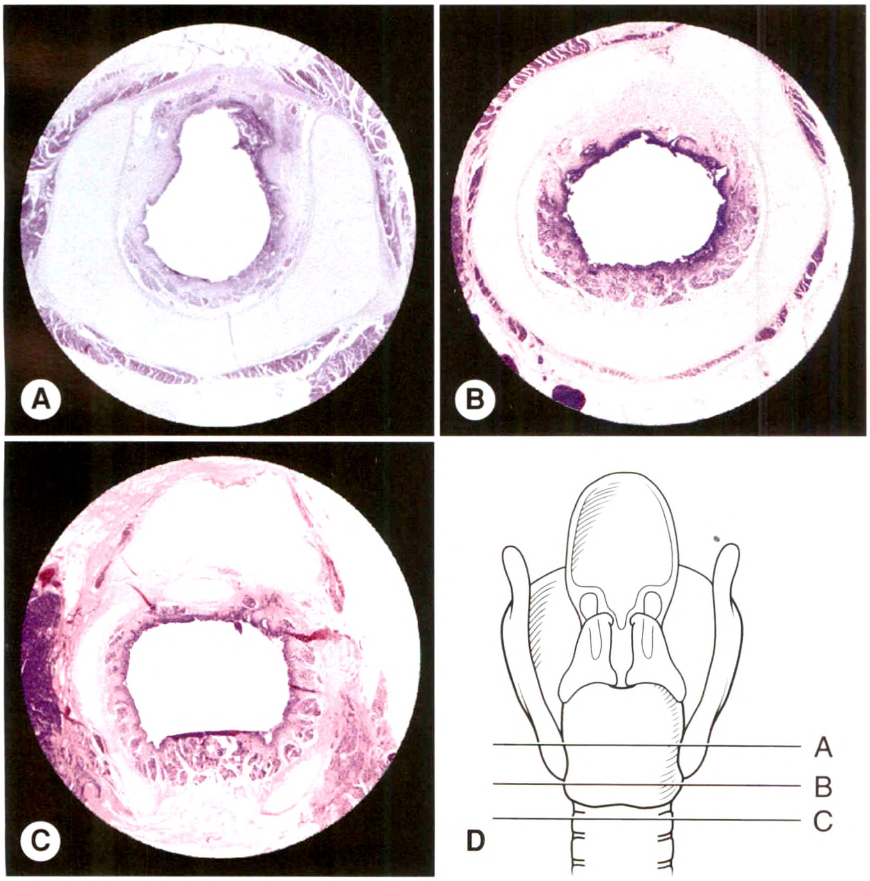


Fig 4. Thickened cricoid cartilage with large anterior lamina. A) Superior, midcricoid level. B) Inferior cricoid level. C) First tracheal ring. Found in association with trapped first tracheal ring, cricoid cartilage is enlarged anteriorly and extends over trapped first tracheal ring, which telescopes up inside cricoid cartilage. Trapped first ring can reduce size of subglottic lumen, contributing to congenital subglottic stenosis. D) Reconstruction indicating approximate level of each section viewed from posterior.

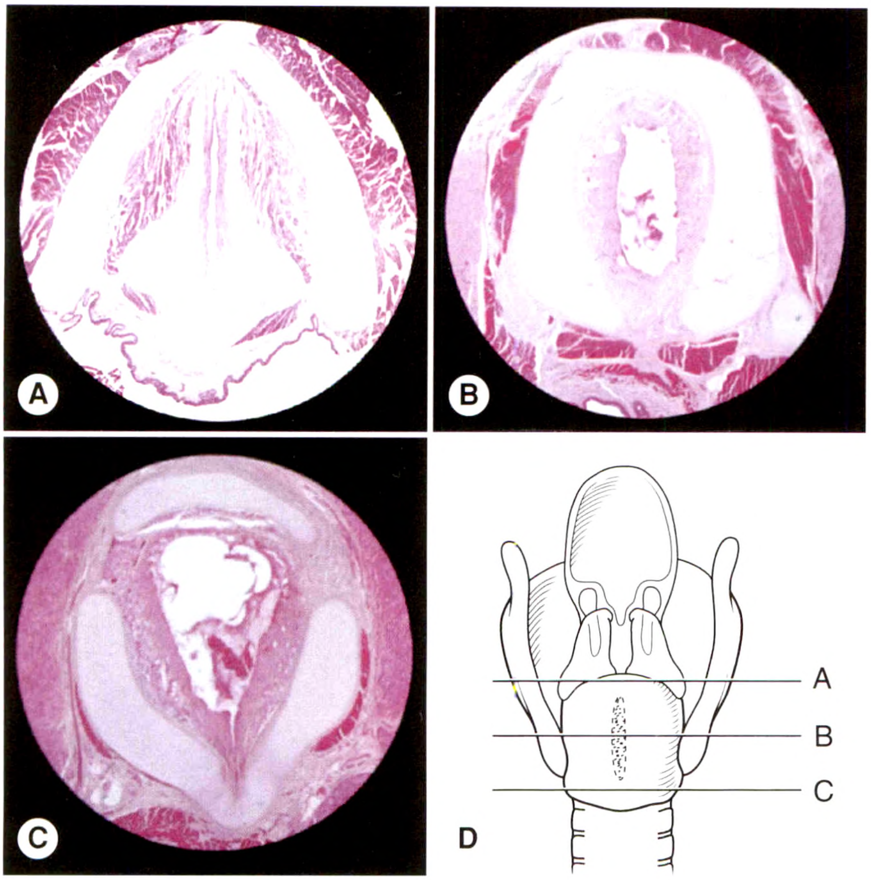


Fig 5. Posterior submucous laryngeal cleft. A) Superior, glottic level. Posterior cricoid lamina is intact but distorted. Interarytenoid muscle is intact. B) Midcricoid level. Submucous cleft of posterior cricoid lamina. Soft tissue is intact. C) Inferior cricoid level. Distorted but complete inferior portion of posterior cricoid ring. Lumen is elliptical. D) Reconstruction of posterior submucous laryngeal cleft indicating approximate level of each section.

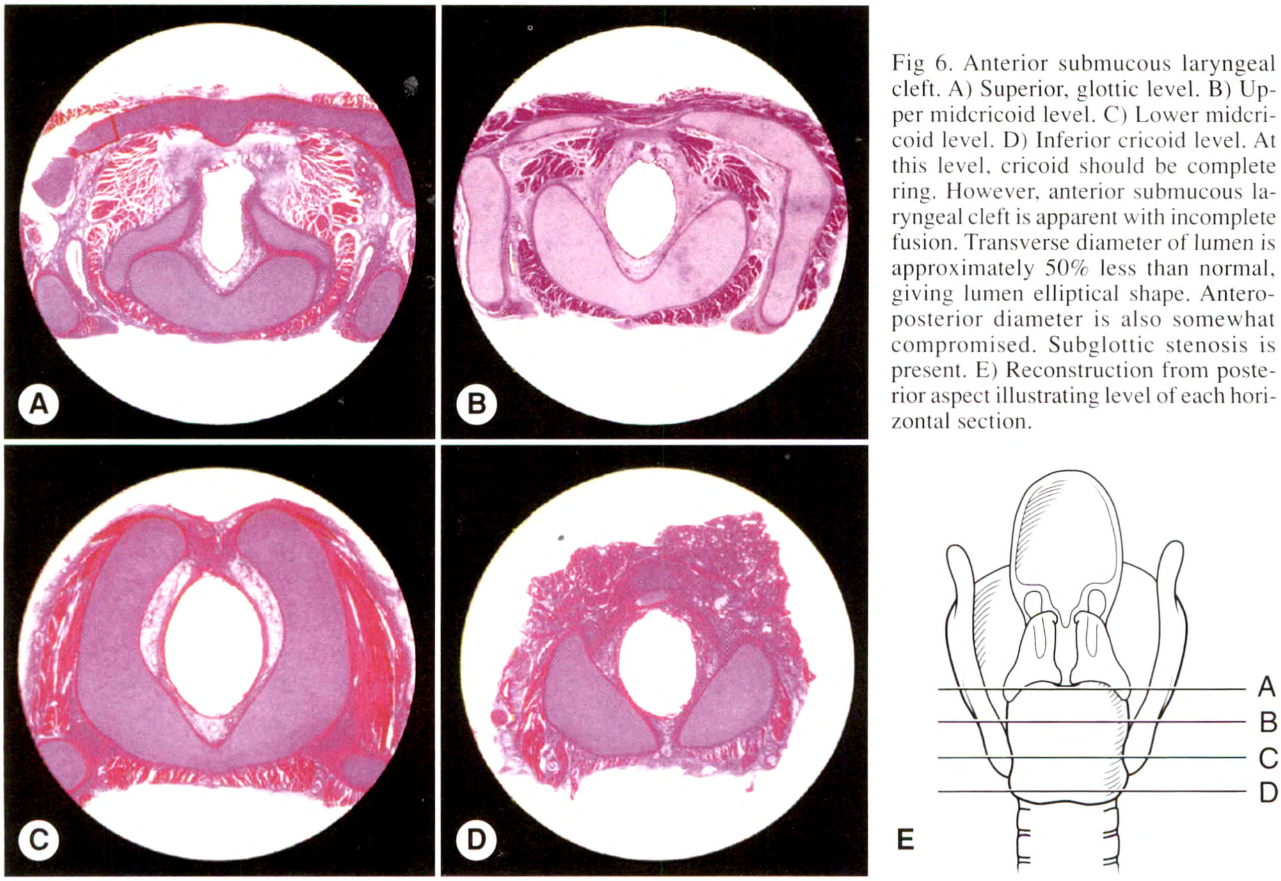


Fig 6. Anterior submucous laryngeal cleft. A) Superior, glottic level. B) Upper midcricoid level. C) Lower midcricoid level. D) Inferior cricoid level. At this level, cricoid should be complete ring. However, anterior submucous laryngeal cleft is apparent with incomplete fusion. Transverse diameter of lumen is approximately 50% less than normal, giving lumen elliptical shape. Anteroposterior diameter is also somewhat compromised. Subglottic stenosis is present. E) Reconstruction from posterior aspect illustrating level of each horizontal section.

PARTIAL POSTERIOR LARYNGEAL CLEFT (PLC II)

The partial laryngeal cleft is distinct from the submucous cleft, in that part of the posterior larynx is cleft through and through to the hypopharynx. The 1 patient with a PLC II was a term female infant with tracheal agenesis who had severe respiratory distress at birth. She had a bronchoesophageal fistula through which she ventilated until she died, shortly after birth. Figure 7 shows that the cleft is continuous through the upper part of the cricoid cartilage, extending inferiorly below the superior surface of the vocal folds. The lower part of the cricoid cartilage is an intact ring. The interarytenoid muscle shows partial agenesis and a fibrous end at the interface of the cleft.

COMPLETE POSTERIOR LARYNGEAL CLEFT (LTEC III, IV)

In the LTEC III, the cleft is continuous through the entire cricoid cartilage and may extend to the thoracic inlet. Two patients had complete PLC (LTEC III). Both developed respiratory distress after birth and required airway intervention. Associated anomalies included tracheoesophageal fistula and congenital subglottic stenosis.

Figure 8 shows a case of LTEC III. Redundant tissue is found on both sides of the cleft; the left is larger than the right and protrudes into the laryngeal lumen. This redundant tissue undoubtedly can contribute to symptoms of upper airway obstruction.[10] The second case of complete laryngeal cleft (LTEC III) was a severe anomaly with no arytenoid cartilage or interarytenoid muscle, and had a deformed cricoid cartilage with thick submucosal fibrosis that caused subglottic stenosis.[11]

Delahunty and Cherry[12] reported 2 cases of complete PLC (LTEC III) and noted atrophic changes of the interarytenoid muscle and lateral subluxation of the cricoarytenoid joint. Lim et al[13] described a case of LTEC III extending to the sixth tracheal ring and noted splaying of the posterior cricoid plate, partial agenesis of the interarytenoid muscle, and incomplete fusion of the tracheal rings.

DISCUSSION

LARYNGEAL CLEFTS (PLC AND LTEC)

Incidence. The PLC, especially LTEC III and IV, has been considered to be rare among congenital anomalies of the larynx. Evans[14] found only 2 cases (0.5%) of PLC in 427 children referred for direct laryngoscopy. In the Division of Pediatric Otolaryngology at The Children's Memorial Hospital, Chicago, from 1990 to 1995, only 7 cases (0.3%) of PLC were diagnosed clinically of the 2,338 patients who underwent diagnostic direct laryngoscopy during this period.[9] However, the incidence of these anomalies is higher among the 122 specimens examined in the Laryngeal Development Laboratory: 9 cases (7.4%) of submucous laryngeal cleft and 3 cases (2.5%) of LTEC. It is likely that we have been missing the endoscopic diagnosis. In 1998, Parsons et al[15] reported 41 cases of PLC I among 660 microlaryngoscopies. Since we began using an operating microscope and suspending an anterior commissure laryngoscope to more carefully examine the posterior glottis, we have identified many more cases of PLC I that previously had been overlooked.

Anatomy. At the level of the epiglottis, the aerodigestive tract divides into the airway anteriorly (larynx) and the hypopharynx posteriorly (Fig 9). The PLC communicates between the larynx and the hypopharynx (not the larynx and esophagus). The inferior anatomic limit of the larynx and hypopharynx is the inferior margin of the cricoid cartilage. The superior extent of the trachea and esophagus is the inferior margin of the cricoid cartilage.

Embryology. According to the Carnegie staging system, the embryonic period has 23 stages of development. At stage 10, the first sign of respiratory system development is seen as a laryngotracheal sulcus. During stage 11, the laryngotracheal groove lengthens and the pulmonary primordium divides into right and left lobes. By stage 12 or 13 (3 to 6 mm and 25 to 28 days), the tracheoesophageal septum makes its appearance. Any vascular compromise or failure of union in forming this septum may result in some degree of tracheoesophageal fistula or LTEC. In stages 14 to 16, there is further pulmonary development and the primitive laryngeal structures appear. In stage 18, the cricoid cartilage develops from 2 lateral centers of chondrification that fuse ventrally at about days 40 to 44, and dorsally at about days 50 to 55.[16]

The specific defect of each LTEC depends on the timing of the damage. Blumberg et al[16] postulated that the formation of the LTEC is caused by an arrest of the cranial advancement of the tracheoesophageal septum and the septal defect's effects on the fusion of the cricoid lamina. Formation of the PLC without a cleft of the tracheoesophageal septum is probably due to defective closure of the cricoid arch.[17]

Classification. Two basic classification systems have been proposed: anatomic and clinical. Pettersson[18] distinguished 3 types of LTEC based on the anatomy. Armitage,[19] an anesthesiologist, introduced

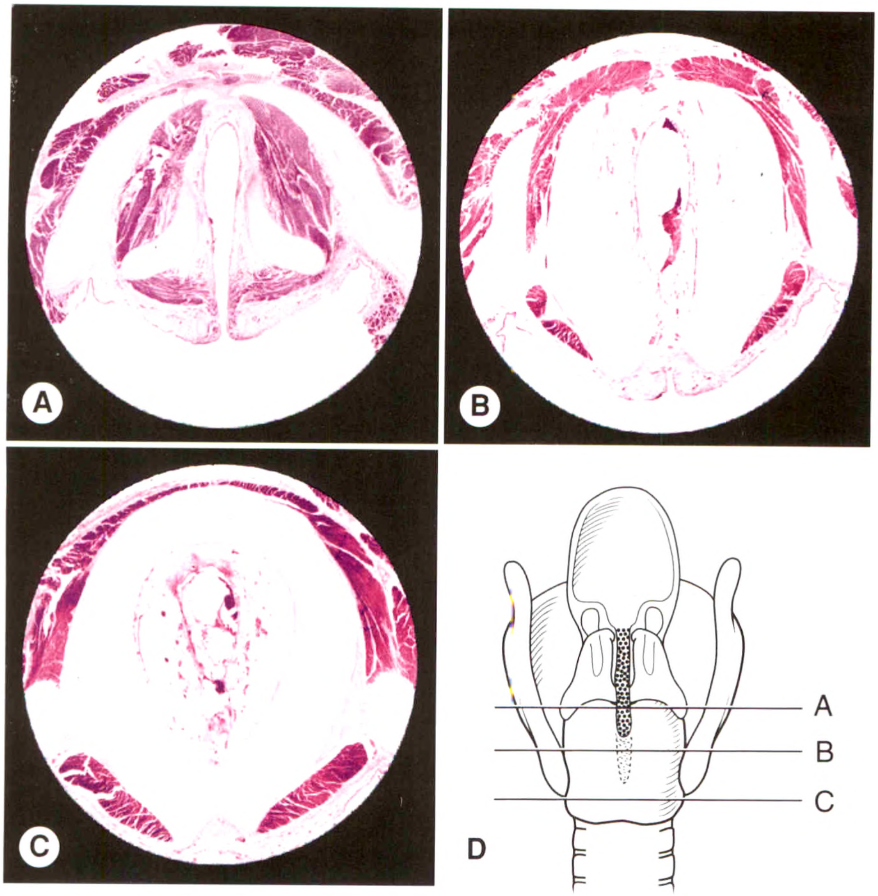


Fig 7. Partial posterior laryngeal cleft (PLC II). A) Superior, glottic level. Interruption of interarytenoid muscle, with separation of respiratory and hypopharyngeal mucosa. B) Midcricoid level. Soft tissue is intact posteriorly, although cartilage is not. C) Inferior cricoid level. This lower part of cricoid cartilage is intact. D) Reconstruction indicating level of each section.

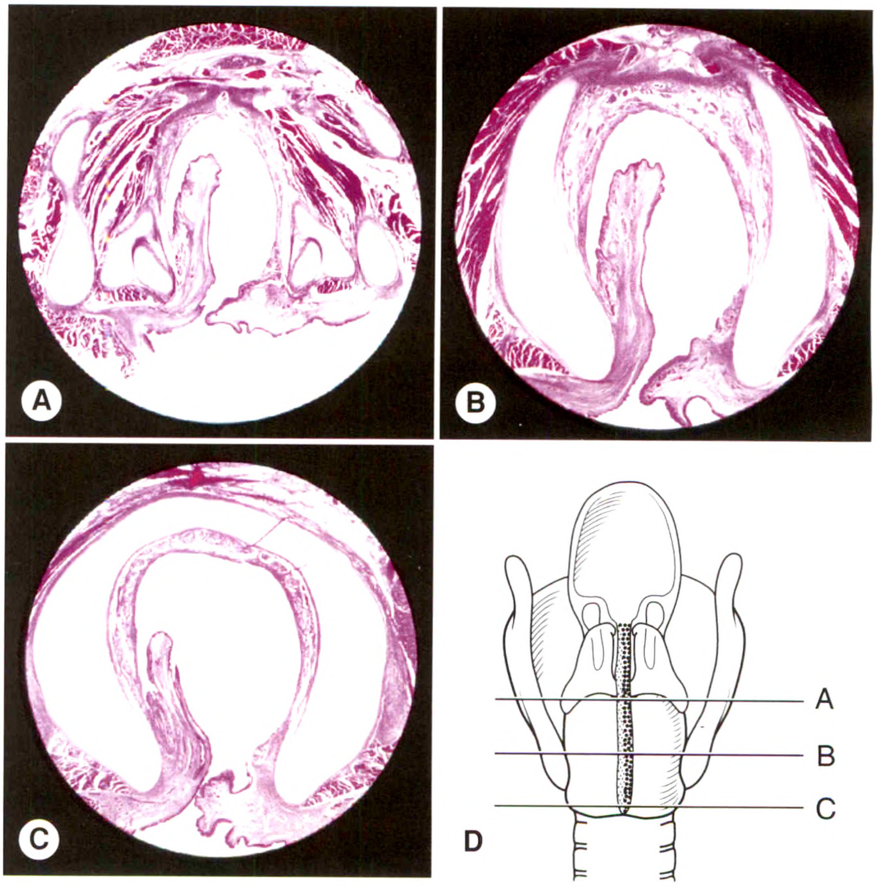


Fig 8. Complete posterior laryngeal cleft (LTEC III). A) Superior, glottic level. Interruption of interarytenoid muscle. Pedunculated hamartomatous mass with small island of cartilage protruding into lumen from left. Cricoid cartilage is completely cleft. B) Midcricoid level. C) Inferior cricoid level. Cricoid cartilage is completely cleft. D) Approximate level of each section is shown in this reconstruction from posterior aspect.

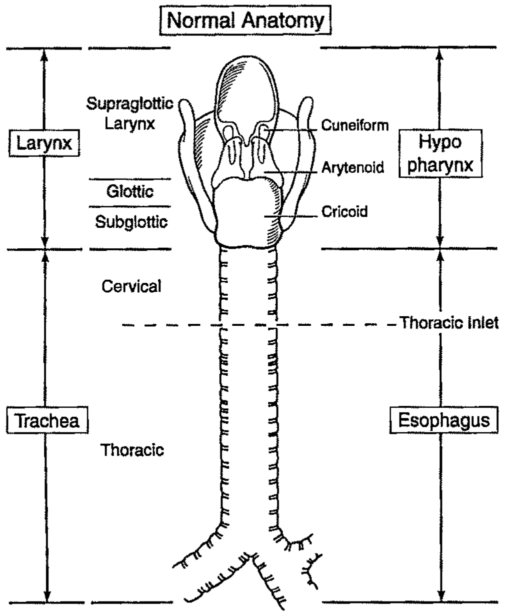


Fig 9. Normal anatomy of larynx and trachea from posterior aspect. Inferior anatomic limit of larynx and hypopharynx is inferior margin of cricoid cartilage.

a modification in 1984 on the basis of 3 cases. Evans[20] proposed a clinically based classification of PLC and LTEC in 1985. Benjamin and Inglis'[21] modification of Evans' classification is probably the most useful. Not only is their proposal well supported, but it is most compatible with information regarding partial cricoid clefts, specifically the submucous ("occult") laryngeal cleft.[9] This classification is illustrated in Fig 10.[9] With the addition of the submucous cleft, the Benjamin and Inglis modification of Evans' classification is anatomically correct and the most clinically relevant.[9]

Type I (PLC I or LTEC I), a supraglottic interarytenoid soft tissue cleft, extends inferiorly no further than the level of the vocal folds. Type II (PLC II or LTEC II), a partial cricoid cleft, extends below the level of the vocal folds, but not to the superior margin of the cricoid ring. Type III is a total cricoid cleft, extending completely through the cricoid cartilage with or without further extension into the cervical tracheoesophageal septum; the thoracic inlet is the inferior limit of the LTEC III. Type IV (LTEC IV) involves a major part of the intrathoracic tracheoesophageal septum; complete extension to the carina creates a common esophageal and tracheal lumen.

Symptoms. The PLC I may be difficult to diagnose. A triad of husky voice, feeding difficulties, and aspiration pneumonia alerts the clinician to the possibility of a cleft larynx.[22] Patients may present with various degrees of respiratory distress, exacerbated or precipitated by attempts at feeding. Stridor may be due to anterior collapse of the posterior supraglottic structures, especially the cuneiform cartilages or the redundant mucosa in the posterior glottic and supraglottic larynx. Coughing, choking, and cyanotic episodes are characteristic.

The severity of symptoms is generally in proportion to the inferior extent of the cleft. Infants with LTEC type III or IV have severe aspiration and cyanosis from birth and develop respiratory distress that is likely to require endotracheal intubation and emergency surgical intervention.

Diagnosis. In evaluating a newborn with problems of choking during feeding, aspiration, increased pharyngeal secretions, and intermittent airway obstruction, the differential diagnosis includes tracheoesophageal fistula, because the symptoms closely mimic those of LTEC. Other anomalies of the aerodigestive tract, such as bilateral choanal atresia, pharyngeal incoordination,[23] vocal fold motion impairment, and gastroesophageal reflux,[24] are also considered.

Direct laryngoscopy (with operating microscope and suspension), bronchoscopy, and esophagoscopy

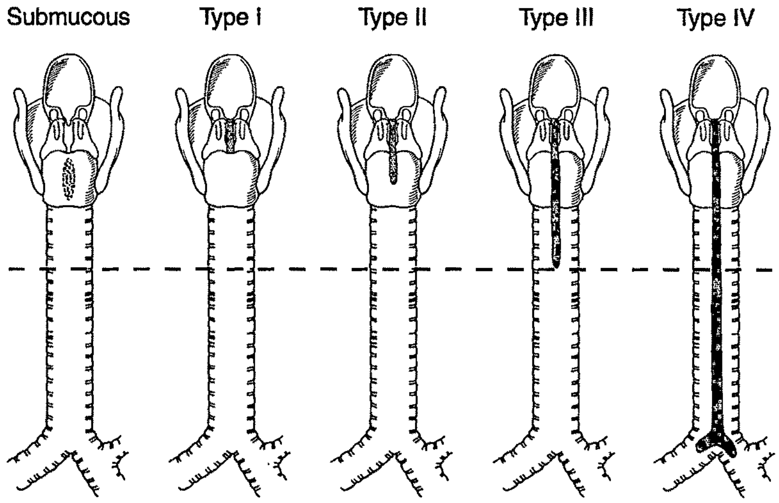


Fig 10. Classification[9] of posterior laryngeal clefts (laryngopharyngeal clefts) and laryngotracheoesophageal clefts.

can make a definitive diagnosis and rule out other anomalies of the larynx and trachea that occur with LTEC. At endoscopy, the lesion is easy to overlook. Even the experienced endoscopist may miss the diagnosis unless there is a high index of suspicion and the PLC is looked for specifically. The endoscopic appearance of the PLC I may resemble that of laryngomalacia. There is often an inward collapse of the posterior supraglottic structures, as well as redundant hypertrophic soft tissue in the posterior glottis. A cleft is best demonstrated with suspension microlaryngoscopy by advancing an anterior commissure laryngoscope between the vocal folds and abducting them widely to visualize the posterior glottis.[25] Identification of the PLC I requires a right-angle probe or an interarytenoid notch height measuring caliper for accurate assessment.[26] In LTEC III and IV, a bronchoscope and an esophagoscope are necessary to determine the inferior extent of the cleft. Twenty percent of patients with laryngeal clefts also have a tracheoesophageal fistula.[16] Subglottic stenosis occurs in a high percentage of larynges with PLC.[9]

ANTERIOR SUBMUCOUS LARYNGEAL CLEFT

The anterior submucous laryngeal cleft is unique. Although this is the first report of a midline submucous cleft of the cricoid cartilage, 3 ventral laryngeal clefts of the thyroid cartilage have been reported.[27,28] None had an associated midline cricoid cartilage cleft.

Symptoms. The infant with the anterior submucous laryngeal cleft reported herein was intubated shortly after birth and ultimately died of cardiorespiratory arrest. Of 3 ventral (thyroid cartilage) clefts reported, 1 was in an infant.[28] She had symptoms of a weak, husky voice. Problems with aspiration eventually resolved.

Diagnosis. The diagnosis of the ventral cleft was made with magnetic resonance imaging.[28] Thickened vocal folds with an anterior glottic web and subglottic swelling were observed at laryngoscopy. The interarytenoid notch was very deep.

CONGENITAL SUBGLOTTIC STENOSIS

Any of the cricoid cartilage deformities described in Table 2 may result in compromise of the subglottic lumen to cause congenital subglottic stenosis. Congenital subglottic stenosis is the second most common cause of stridor in neonates, infants, and children.[29]

Symptoms. Symptoms of upper airway obstruction predominate. Stridor is biphasic or primarily inspiratory. Recurrent or persistent croup is typical, particularly in children younger than 6 months of age. "There is no such thing as croup under 1 year of age" is a dictum that serves as a reminder that laryngeal anomalies frequently are first symptomatic with a common respiratory tract infection. The edema and thickened secretions of a common cold further narrow the already compromised airway. The infant has the classic barking cough, stridor, and fever typical of croup. Pneumonia or atelectasis may be secondary to congenital subglottic stenosis.

Diagnosis. Occasionally the diagnosis is made by standard posteroanterior and lateral airway radiographs. The diagnosis is confirmed at endoscopy. An anterior commissure laryngoscope is used to separate the vocal folds gently to allow careful inspection and palpation of the subglottic larynx. A bronchoscope, dilator, or endotracheal tube is used to gauge objectively the size of the laryngeal lumen. The subglottis is inspected with a fine telescope, which is then passed through the narrowing so that the trachea and bronchi can be examined for concomitant problems. An endotracheal tube that will pass comfortably through the subglottic stenosis is placed. A tube is chosen so that the audible leak pressure is between 10 and 25 cm H_2O. Comparison is made to the expected normal size for age in the chart developed by Myer et al.[30]

FRAGMENTED, DISTORTED, OSSIFIED CRICOID

A fragmented and distorted cricoid cartilage has been identified in 8 specimens, all of which had been intubated. Some areas of ossification are present. The mean duration of tracheal intubation of these patients was approximately 8 weeks. Therefore, it is likely that these represent acquired rather than congenital lesions.[11,31] A detailed discussion is not within the scope of this study.

CONCLUSIONS

In order to plan rational therapy, it is important for the clinician to have a clear understanding of congenital cricoid cartilage abnormalities. Subglottic stenosis that compromises the lumen by 50% or less is surprisingly easy to overlook. Further, a cursory laryngoscopic examination of the larynx will miss a laryngeal cleft. Specific endoscopic techniques are important for accurate observation and diagnosis. Objective measurement, especially endotracheal tube sizing to determine the precise size of the subglottic larynx, will accurately calibrate the lumen and rule out subglottic stenosis.[30] Using an anterior commissure laryngoscope, inspecting the posterior glottis with the operating microscope, and palpating with a right-angle probe will decrease the likelihood of overlooking a PLC.[15]

ACKNOWLEDGMENT — The larynx with the anterior submucous laryngeal cleft was procured for the laboratory by Robert P. Miller, MD, Chicago, Illinois.

REFERENCES

1. Tucker GF, Tucker JA, Vidic B. Anatomy and development of the cricoid. Serial-section whole organ study of perinatal larynges. Ann Otol Rhinol Laryngol 1977;86:766-9.

2. Holinger PH, Johnson KC, Schiller F. Congenital anomalies of the larynx. Ann Otol Rhinol Laryngol 1954;63:581-606.

3. McMillan WG, Duvall AJ. Congenital subglottic stenosis. Arch Otolaryngol 1968;87:70-6.

4. Sayre JW, Hall EG. Anomalies of the larynx associated with tracheoesophageal fistula. Pediatrics 1954;13:150-4.

5. Fearon B, Cotton R. Subglottic stenosis in infants and children: the clinical problem and experimental surgical correction. Can J Otolaryngol 1972;1:281-9.

6. Tucker JA, O'Rahilly R. Observations on the embryology of the human larynx. Ann Otol Rhinol Laryngol 1972;81:520-3.

7. Tucker GF, Ossoff RH, Newman AN, Holinger LD. Histopathology of congenital subglottic stenosis. Laryngoscope 1979;89:866-76.

8. Tucker GF Jr, Maddalozzo J. "Occult" posterior laryngeal cleft. Laryngoscope 1987;97:701-4.

9. Moungthong G, Holinger LD. Laryngotracheoesophageal clefts. Ann Otol Rhinol Laryngol 1997;106:1002-11.

10. Holinger LD, Tansek KM, Tucker GF Jr. Cleft larynx with airway obstruction. Ann Otol Rhinol Laryngol 1985;94:622-6.

11. Chen JC, Holinger LD. Congenital laryngeal lesions: pathology study using serial macrosections and review of the literature. Pediatr Pathol 1994;14:301-25.

12. Delahunty JE, Cherry J. Congenital laryngeal cleft. Ann Otol Rhinol Laryngol 1969;78:96-106.

13. Lim TA, Spanier SS, Kohut RI. Laryngeal clefts. A histopathologic study and review. Ann Otol Rhinol Laryngol 1979;88:837-45.

14. Evans JNG. Laryngotracheoplasty. Otolaryngol Clin North Am 1977;10:119-23.

15. Parsons DS, Stivers FE, Giovanetto DR, Phillips SE. Type I posterior laryngeal cleft. Laryngoscope 1998;108:403-10.

16. Blumberg JB, Stevenson JK, Lemire RJ, Boyden LA. Laryngotracheoesophageal cleft, the embryologic implications: review of the literature. Pediatr Surg 1965;56:559-66.

17. Roth B, Rose KG, Bohn GB, Gunter H. Laryngotracheoesophageal cleft. Eur J Pediatr 1983;140:41-6.

18. Pettersson G. Inhibited separation of larynx and the upper part of trachea from oesophagus in a newborn: report of a case successfully operated upon. Acta Chir Scand 1955;10:250-4.

19. Armitage EN. Laryngotracheoesophageal cleft. Anaesthesia 1984;39:706-13.

20. Evans JNG. Management of the cleft larynx and tracheoesophageal clefts. Ann Otol Rhinol Laryngol 1985;94:627-30.

21. Benjamin B, Inglis A. Minor congenital laryngeal clefts: diagnosis and classification. Ann Otol Rhinol Laryngol 1989;98:417-20.

22. Pillsbury HC, Fischer ND. Laryngotracheoesophageal cleft: diagnosis, management, and presentation of new diagnostic device. Arch Otolaryngol 1977;103:735-7.

23. Evans KL, Courteney-Harris R, Bailey M, Evans JNG, Parsons DS. Management of posterior laryngeal and laryngotracheoesophageal clefts. Arch Otolaryngol Head Neck Surg 1995;121:1380-5.

24. Cohen SR. Cleft larynx. A report of seven cases. Ann Otol Rhinol Laryngol 1975;84:747-56.

25. Green CG, Holinger LD, Gartlan MG. Technique. In: Holinger LD, Lusk RP, Green CG, eds. Pediatric laryngology and bronchoesophagology. New York, NY: Lippincott-Raven Press, 1997:97-116.

26. Bent JP, Bauman NM, Smith RJH. Endoscopic repair of type IA laryngeal clefts. Laryngoscope 1997;107:282-6.

27. Schild JA, Mafee MF. Ventral cleft of the larynx in an adult. Case report. Ann Otol Rhinol Laryngol 1989;98:66-9.

28. Cohen SR, Thompson JW. Ventral cleft of the larynx: a rare congenital laryngeal defect. Ann Otol Rhinol Laryngol 1990;99:281-5.

29. Holinger LD. Etiology of stridor in the neonate, infant and child. Ann Otol Rhinol Laryngol 1980;89:397-400.

30. Myer CM III, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Rhinol Laryngol 1994;103:319-23.

31. Liu H, Chen JC, Holinger LD, Crussi FG. Histopathologic fundamentals of acquired laryngeal stenosis. Pediatr Pathol Lab Med 1995;15:655-77.

Ann Otol Rhinol Laryngol 108:1999

EFFECT OF INTRAVENOUS SUBSTANCE P ON LARYNGEAL ADDUCTOR ACTIVITY IN YOUNG DOGS

NANCY M. BAUMAN, MD
IOWA CITY, IOWA

DEQIANG WANG, MD
IOWA CITY, IOWA

DEBRA M. JAFFE, MD
IOWA CITY, IOWA

ANTHONY D. SANDLER, MD
IOWA CITY, IOWA

ERICH S. LUSCHEI, PHD
SEATTLE, WASHINGTON

Reflex laryngeal adduction is a component of both the laryngeal chemoreflex and the esophagolaryngeal adductor reflex, two life-threatening reflexes that occur in immature animals. These two reflex responses are also thought to exist in infants and may play a role in causing life-threatening laryngospastic events and perhaps sudden infant death syndrome. Identifying neurotransmitters that mediate laryngeal adduction is important to understanding the mechanism of reflex laryngeal responses and to identifying potential means of pharmacologic prevention. Substance P (SP), a tachykinin, putatively functions as a sensory neurotransmitter and may play a role in mediating laryngeal reflexes. Substance P–immunoreactive–like fibers and receptors are present in the subepithelial tissues of the larynx, the vagus nerves, the nodose and jugular ganglia, and the vagal brain stem nuclei. In this investigation, the effect of SP infusion on laryngeal motor activity in an in vivo model is reported. Substance P was infused intravenously into 8 puppies (20 to 133 days of age, mean 81.2), on a mean of 3.0 occasions (range 1 to 6). Cardiovascular, respiratory, arterial blood gas, and cricothyroid (CT), thyroarytenoid (TA), and genioglossus electromyographic (EMG) responses to infusion of the tachykinin were recorded and subsequently analyzed. The SP infusion induced a marked increase in CT or TA EMG activity in 23 of 24 studies, and the increase was typically apparent within 60 seconds of the infusion. An increase in genioglossus EMG activity did not occur. An immediate, profound decrease in mean arterial pressure and an increase in respiratory rate and depth of chest wall excursion accompanied the laryngeal response. Arterial blood gas values remained unchanged ($p > .05$). The laryngeal adductor response to SP infusion was blocked when animals were pretreated with a systemic SP antagonist (Pfizer CP-96,345). This study demonstrates that peripheral infusion of the tachykinin SP induces a marked increase in laryngeal adductor activity. The response may be blocked by pretreatment of animals with a systemic SP antagonist. Because SP is thought to act primarily as a sensory neurotransmitter, these findings may be important in understanding the mechanism of reflex laryngeal adductor responses.

KEY WORDS — esophagolaryngeal adductor reflex, laryngeal adduction, laryngeal chemoreflex, laryngospasm, substance P, tachykinin.

INTRODUCTION

Reflex laryngeal adduction is a component of the laryngeal chemoreflex and the esophagolaryngeal adductor reflex and is mediated by activation of the cricothyroid (CT) and thyroarytenoid (TA) muscles.[1,2] These two reflex responses have been identified in laboratory animals and may prove life-threatening if elicited during a critical period of immaturity. Both reflexes are thought to occur in infants and are of clinical interest, as postmortem studies indicate that laryngospasm is the final fatal event of many victims of sudden infant death syndrome.[3-5] Identifying neurotransmitters that mediate laryngeal adduction may advance our understanding of reflex laryngeal responses and ultimately disclose new treatment options for laryngospastic events.

Substance P (SP) is a member of the family of tachykinins, a group of biologically active peptides that share the common C terminal end amino acid sequence Phe-X-Gly-Leu-Met-NH_2, and may play a role in mediating laryngeal reflex responses.[6] The neurotransmitter was first identified in 1931[7] and since that time has been the subject of many investigations to determine its distribution and function. Substance P serves a multitude of functions, but primarily acts as a sensory neurotransmitter. The pep-

---

From the Department of Otolaryngology–Head and Neck Surgery, Pediatric Division (Bauman, Wang, Jaffe), the Department of Surgery, Pediatric Division (Sandler), and the Wendell Johnson Speech and Hearing Center (Luschei), The University of Iowa College of Medicine, Iowa City, Iowa. This research was supported by National Institutes of Health grant 5 KO8 DC00129-02. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The University of Iowa.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 11-12, 1998. Recipient of the Broyles-Maloney Award.

CORRESPONDENCE — Nancy M. Bauman, MD, Dept of Otolaryngology–Head and Neck Surgery, The University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Iowa City, IA 52242.

tide is synthesized in cell bodies and stored in nerve terminals of sensory neurons.[8]

Substance P has been identified in the cerebral cortex, the brain stem, and the peripheral nervous system. It is often colocalized with other neurotransmitters such as calcitonin gene–related peptide.[9] In animals, SP plays an important role in integrating the cardiovascular, behavioral, and endocrine responses to stress, and it is thought to function similarly in humans.

Immunocytochemistry has identified SP-like immunoreactivity (SP-IR) in the larynx, the vagus nerve, the nodose and jugular ganglia, and the sensory and motor brain stem nuclei of the vagus nerve.[9] Despite the pervasive presence of SP in the larynx and its innervating system, the effect of the tachykinin on laryngeal activity has not been extensively studied. This investigation explores the effect of systemic perfusion of SP in dogs on the activity of the most pronounced laryngeal adductor muscles, the CT and TA muscles.

MATERIALS AND METHODS

Eight purpose-bred, mixed-breed puppies were anesthetized with intravenous pentobarbital sodium (30 mg/kg). One third of the initial dose was subsequently administered every 30 to 40 minutes to maintain an appropriate level of anesthesia as determined by the absence of purposeful movements and corneal reflexes. Animals breathed spontaneously during the testing procedures, but were sometimes intubated and mechanically ventilated for a short period of time during the surgical preparation.

Systemic blood pressure and heart rate were measured via a femoral arterial catheter line placed percutaneously, or through a small cutdown incision, and connected to an external pressure transducer. Respiratory rate was measured by belt pneumotachography or by diaphragm (DP) electromyographic (EMG) activity monitored with a bipolar electrode inserted through a substernal 2-cm incision. The amplified signals were simultaneously transmitted to an audio speaker for auditory monitoring and a computer terminal for on-line visual monitoring, monitored on-line, recorded, and transferred to a magnetico-optical disk for subsequent analysis.

Bipolar hooked wire electrodes were placed unilaterally into the CT and TA muscles for EMG recordings. Electrodes were placed under direct vision into the CT muscle, exposed by a 2-cm horizontal cervical incision over the cricoid cartilage. Electrodes were placed into the TA muscle by passing the needle cannula through the CT membrane and directing it superiorly into the muscle. The needle cannula was removed after verifying its presence in the TA muscle by direct laryngoscopy. Bipolar hooked wire electrodes were also placed in the genioglossus muscle to monitor tongue motor activity. All electrodes were connected to the voltage-pulse input coupler of the recorder, the signals were amplified and digitized, and EMG activity was monitored on-line via a computer display. Proper electrode placement was confirmed by the phasic audible EMG signal in relationship to the respiratory cycle. Activity was recorded on a computer hard drive (Gateway 2000, 4DX2-66V) using CODAS WINDAQ software (Akron, Ohio) at a sampling rate of 1,125 samples per second per channel and viewed on-line on a computer terminal (Gateway 2000, Crystal Scan).

Physiologic body temperature was maintained with a warming blanket. All procedures were approved by the Institutional Animal Research Committee and were in accordance with guidelines set forth by the National Institutes of Health.

Baseline cardiorespiratory and laryngeal EMG recordings were obtained. Substance P (1 μg/kg) was infused intravenously, and its effect on cardiorespiratory and laryngeal EMG tracings was recorded for subsequent comparison to the baseline recordings. We administered 1 μg/kg because this was the lowest dose that consistently induced laryngeal adductor activity when dose-response curves utilizing 0.01 to 10 μg/kg were established in our laboratory (unpublished data). Arterial blood gas recordings were obtained before infusion of SP and shortly after infusion of SP, when the blood pressure was at its nadir. Results of SP infusions before and after administration of an SP antagonist specific for the NK-1 receptor (SPA; CP-96,345, 1.0 mg/kg) were also recorded and compared.

RESULTS

Substance P (1 μg/kg) was intravenously infused into 8 dogs ranging in age from 20 to 133 days (mean 81.2 days). Animal weights ranged from 2.0 to 12.2 kg (mean 6.5 kg). All animals survived following the infusions and underwent a total of 24 studies (range 1 to 6) with a minimum of 1 week allowed to elapse between investigations. Results are summarized in Table 1.

Cardiorespiratory Effects. Substance P infusion (1 μg/kg) elicited an immediate and profound decrease in mean arterial pressure (MAP) in all animals. The MAP subsequently increased, but values remained below baseline (Fig 1).

Respiratory rate increased following infusion of the tachykinin in 23 animals (Fig 1) and remained unchanged in 1 animal. The increase occurred a mean

TABLE 1. SUMMARY OF RESPONSE TO SUBSTANCE P IN 24 STUDIES IN DEVELOPING DOGS

	Increased	*Decreased*	*Unchanged*	*Time (s)**
MAP		24		16.0
RR	23		1	22.6
CT EMG	20		4	43.6
TA EMG	20	2	2	91.4
Genioglossus EMG			24	N/A

MAP — mean arterial pressure, RR — respiratory rate, CT — cricothyroid, EMG — electromyography, TA — thyroarytenoid, N/A — not applicable.

*Mean time to onset of response.

of 22.6 seconds after initiation of SP infusion. A belt pneumotachograph and DP EMG were both used to monitor the respiratory response in 9 animals. In 6 of these animals, the depth of respirations monitored by the belt increased despite a decrease (4 animals) or no change (2 animals) in the magnitude of DP EMG activity; this finding suggested that recruitment of the intercostal muscles accounted for the increase in chest wall excursion.

Laryngeal Electromyographic Activity. Baseline laryngeal EMG activity varied between animals and in the same animals on different study days. Baseline CT EMG activity was present in all studies and occurred at the start of inspiration, usually preceding the DP EMG activity by a fraction of a second (Figs 2 and 3). Cricothyroid EMG activity was not noted during expiration in any of the animals. Baseline TA EMG activity was present in only 17 of the 24 studies and usually occurred during inspiration, although in 6 animals, it occurred during expiration.

Cricothyroid muscle activity increased following SP infusion in 20 of the 24 studies, and remained unchanged in 4 studies. The increase in CT activity occurred a mean of 43.6 seconds after infusion (range 13 to 100 seconds; Fig 2). Both the magnitude and duration of CT EMG activity increased following SP infusion. In marked responses, electrical activity of the CT muscle was even evident during the expiratory phase of respiration (Fig 2).

Thyroarytenoid muscle activity increased following SP infusion in 20 studies, decreased in 2, and remained unchanged in 2. The magnitude of the increase in electrical activity was typically less than that of the CT muscle (Fig 4) and began 91.4 seconds (mean) after infusion and usually followed the response of the CT muscle. Thyroarytenoid activity during baseline respirations was absent in 7 animals, but appeared following infusion of SP.

Substance P infusion induced an increase in CT *or* TA EMG activity in 23 of the 24 studies. The response to SP infusion in animals was present even when serial infusions were completed during the same study day. The EMG activity sometimes remained mildly increased for over an hour after SP infusion. An increase in electrical activation of the CT muscle was demonstrated to still occur in 1 animal following the fourth infusion of SP (Fig 3).

Activation of the genioglossus muscle did not occur following SP infusion, as noted by an absence of a registered EMG signal from the hooked wire electrode (Figs 1-4) and an absence of gross motor activity under direct visualization.

Arterial Blood Gas Results. Arterial blood gases were determined before and after SP infusion in 5

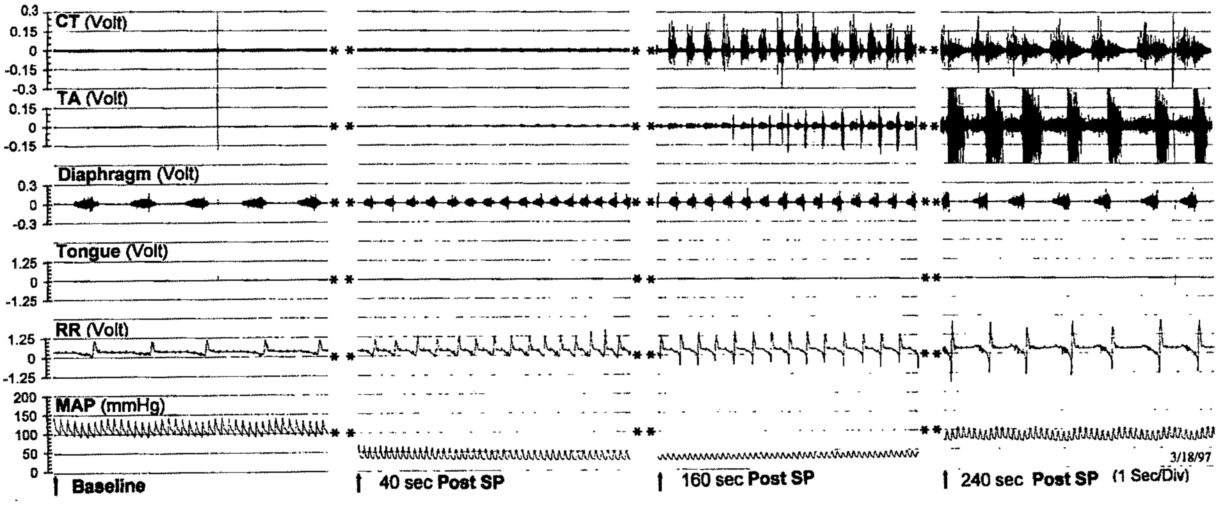


Fig 1. Tracing from 72-day-old, 6.4-kg puppy before and after intravenous substance P (SP) infusion (1 µg/kg). Note increase in cricothyroid (CT) and thyroarytenoid (TA) electrical activity evident 40 seconds after SP infusion. Respiratory rate (RR), as monitored by belt pneumotachograph and diaphragm (DP) electromyographic (EMG) activity, increases. Mean arterial pressure (MAP) decreases significantly immediately following SP infusion and subsequently returns to near-baseline level. Note absence of tongue EMG activity.

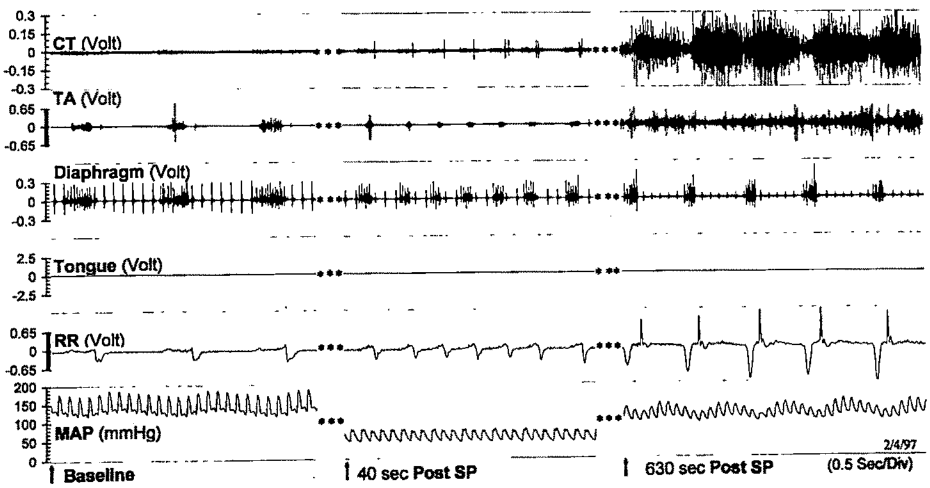


Fig 2. From 133-day-old, 12.2-kg puppy before and after SP infusion (1 μg/kg). SP increases magnitude of CT and TA electrical activity during both inspiration and expiration. Expiration correlates with absence of DP EMG activity. (Note heart rate artifact on DP tracing during expiration.) Increase in CT activity precedes increase in TA activity and is noted 40 seconds following SP infusion. Although depth of respirations increases, magnitude of DP EMG activity remains relatively unchanged, suggesting that recruitment of other muscles of respiration has occurred.

animals during 10 of the studies. Mean pH, PCO2, and PO2 values were compared by the paired Student's *t*-test and were not significantly altered by SP infusions (p > .05; Table 2).

Substance P Antagonist Studies. Substance P infusions were performed in 6 studies before and immediately after the animals were treated with SPA (CP-96,345, 1.0 mg/kg). Animals were a mean of 84.3 days of age (range 72 to 93 days) and weighed a mean of 7.8 kg (range 6.4 to 9.0 kg). Infusion of SP induced an increase in both CT and TA activity in all 6 studies. When the animals were pretreated with SPA, subsequent SP infusion failed to elicit an increase in CT or TA activity. Additionally, the characteristic marked decrease in MAP following SP infusion was markedly blunted in severity and in duration in the presence of the SPA.

DISCUSSION

In this investigation, systemic infusion of SP induced a marked increase in electrical activity of the CT or the TA adductor muscles of the canine larynx in 23 of 24 trials. This marked laryngeal response to SP infusion has not been previously reported in an in vivo study. Application of excitatory neurotransmitters to the periaqueductal gray area elicits phonation in decerebrate anesthetized cats,[10] and electrical stimulation of the periaqueductal gray area in anesthetized dogs elicits phonation,[11] but, to our knowledge, an increase in laryngeal motor activity from systemic infusion of a neurotransmitter, in the absence of laryngeal stimulation, has not been reported.

The mechanism of action of SP's excitatory effect on laryngeal adductor activity is unknown. Immunocytochemistry has revealed SP-IR in the larynx and in both the peripheral and central components of the vagal system in human and nonhuman animals.[12,13] Potential site(s) of action explaining the laryngeal adductor response seen in this investigation include the neuromuscular end plate, the vagal ganglia, and one or more of the vagal brain stem nuclei. Substance P is a putative sensory neurotransmitter, and its marked effect on laryngeal motor activity may be explained as a reflex efferent (motor) response to afferent (sensory) stimulation. Potential sites of SP's effect on laryngeal adductor activity are presented below. It is interesting to note that al-

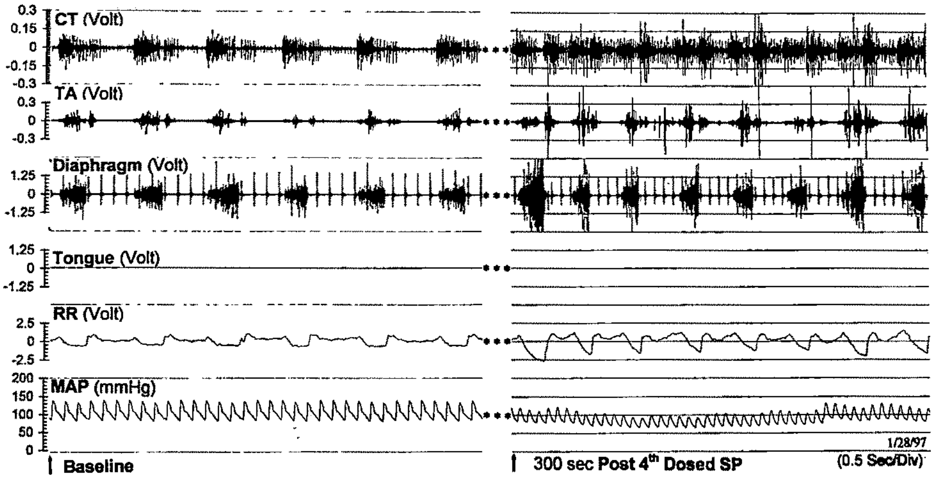


Fig 3. Tracing from 126-day-old, 11.2-kg puppy before and after fourth SP infusion (1 μg/kg). Note that electrical activity of CT and TA muscles increases even following fourth dose of SP (1 μg/kg). Baseline CT and TA activity remain increased 40 minutes after third dose of SP.

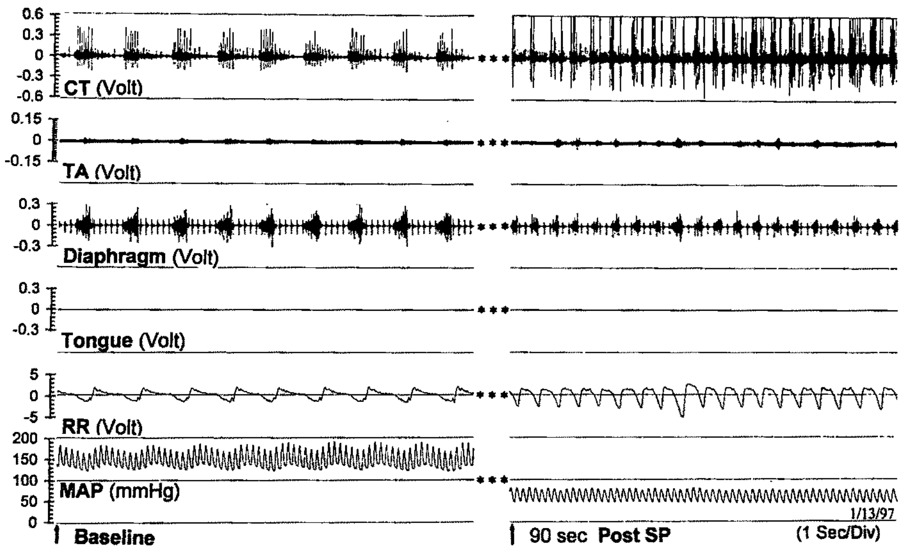


Fig 4. Tracing from 100-day-old, 8.8-kg puppy before and after SP infusion (1 µg/kg). Note that 90 seconds after infusion of SP, CT electrical activity increases in magnitude, while TA activity remains relatively unchanged.

though calcitonin gene–related peptide is often co-localized with SP in the larynx and the vagal nerve system, studies in our laboratory have demonstrated that infusion of that peptide does not alter laryngeal motor activity (unpublished data).

Neuromuscular End Plate. Substance P–like immunoreactivity is present in the larynx of humans[14,15] and in many animal models, including dogs[16] and cats.[17] It is unlikely that the tachykinin exerts its laryngeal adductor effect directly at the neuromuscular end plate. Although SP-IR is present in the lamina propria of the larynx, particularly the epiglottis and subglottis, it is not present in the vocal cords themselves. The peptide is located in nerve endings and taste bud–like structures and most likely regulates mucus secretion, allergic reactions, and circulatory responses. In preliminary studies performed in our laboratory, SP infusion, following superior laryngeal nerve transection, failed to elicit CT motor activity, but still elicited TA activity (unpublished data). If SP functioned as a systemic neurotransmitter (neurohormone) at the motor end plate, both adductor muscles still should have been activated despite transection of the superior laryngeal nerve.

Nodose and Jugular Ganglia. Other potential sites of origin explaining SP's laryngeal effect include the nodose and jugular vagal ganglia and the corresponding brain stem nuclei. Substance P–like immunoreactivity is present in 10% to 30% of cell bodies of the nodose and jugular ganglia in monkeys.[18,19] It is possible that the systemic infusion of SP in this investigation mimicked the release of SP from these neurons and elicited a vagal afferent-efferent response that activated the laryngeal adductor muscles.

TABLE 2. ARTERIAL BLOOD GAS RESULTS BEFORE (BASELINE) AND AFTER SUBSTANCE P INFUSION IN 10 STUDIES PERFORMED IN 5 ANIMALS

	pH	*P_{O2} (mm Hg)*	*P_{CO2} (mm Hg)*
Baseline	7.21	86.2	43.8
After substance P infusion	7.22	83.7	42.4
p	.59	.72	.47

Results are means. Substance P infusion did not significantly alter pH, P_{O2}, or P_{CO2} values.

Vagal Nuclei. Substance P–like immunoreactivity has also been identified in the sensory vagal nuclei of the brain stem medulla in both human[20] and nonhuman animals,[21,22] including the dog.[23] It is reasonable to assume that peripherally administered SP gains access to the central nervous system, as the concentration of SP in the cerebrospinal fluid correlates closely with serum levels.[24] Intricate connections exist between the primary afferent (nucleus tractus solitarius [NTS]) and the primary efferent (nucleus ambiguus [NA]) nuclei of the laryngeal control system.[25] Input into the NA from the NTS has been shown to be important in coordinating respiration and swallowing.[26] If systemic SP administration mimics the release of SP by the afferent system, these connections may explain the resultant laryngeal motor activity seen in this investigation. Indeed, the NTS is one of the most densely staining regions for SP in the canine dorsomedial medulla[23] and is the primary site of synapse of vagal sensory neurons, whose cell bodies are located in the nodose ganglion.[27] Up-regulation of SP receptors in the NTS has been shown to follow ipsilateral excision of the nodose ganglion in cats.[28] The paraventricular and ventromedial nuclei, which also provide input into vagal nuclei and demonstrate SP-IR,[29] may also play a role in mediating the laryngeal response seen in this investigation.

Motor neurons arising from the NA innervate the intrinsic muscles of the larynx and are organized topographically. Neurons in the rostral-ventral aspect of the nucleus innervate the CT muscle, and those in the dorsal-caudal region innervate the TA muscle.[30] Projections to the NA that likely modulate its motor activity arise from multiple sites, including the cerebral cortex, the periaqueductal gray area, the parabrachial nucleus, the reticular formation, the nucleus retroambiguus, and the NTS.[12,25,30,31] Substance P–like immunoreactive fibers were found in the NA of postmortem pediatric patients (4 weeks to 22 months of age), but were present in far greater concentration in the NTS.[32]

To determine which of these potential site(s) best explains SP's mechanism of laryngeal adductor activation, we plan to complete additional transection studies and stereotactic injection of SP into select brain stem nuclei. Other studies assessing the physiologic effect of SP on cardiovascular and respiratory parameters have shown that the tachykinin's activity varies markedly depending on its site of application. For example, peripheral administration of SP causes an immediate and profound decrease in MAP due to a direct vasodilatory action, but, in marked contrast, intracerebroventricular injection reportedly elicits hypertension.[33] Similarly, microiontophoretic application of SP to single neurons of the NTS elicits an excitatory effect on the respiratory system, but intracisternal injections of the tachykinin elicit an inhibitory effect.[34] It seems reasonable to suggest that the NTS is the most likely site to mediate SP's effect on the laryngeal adductor muscles, insofar as the tachykinin is thought to function chiefly as a sensory neurotransmitter.

Substance P administration in this investigation failed to elicit electrical activity in the genioglossus muscle, despite the known presence of SP-IR in the hypoglossal nucleus.[35] The hypoglossal nucleus is purely a motor nucleus and lacks sensory components. Perhaps this finding further supports the belief that motor activity from SP administration occurs as a reflex response to sensory stimulation. This observation also demonstrates that the excitatory effect of SP is directed to laryngeal adductor muscles and is not a general excitatory effect on brain stem–controlled motor systems.

The presence and magnitude of the laryngeal response to SP infusion varied between the animals and within the animals that were studied on multiple occasions. We attempted to find a cause for this varied activity. Because human fetal studies have demonstrated that SP-IR appears in the NTS between 11 and 16 weeks of gestational age and that the density of SP-IR changes during the gestational period,[20] we attempted to correlate the age of the animal in our investigations with the presence or magnitude of the laryngeal adductor response to SP infusion. We were unable to note an association and found some animals to demonstrate a stronger adductor response at a younger age, while other animals showed a more pronounced effect at an older age. Perhaps the magnitude of change could not be correlated with animal age because all of the young dogs in this study were relatively close in age (1 to 4 months). Previous studies in our laboratory have shown that SP infusion also induces an increase in laryngeal motor activity in adult dogs (greater than 1 year of age), although the magnitude of the increase appeared less pronounced than that seen in the immature animals in this study (unpublished data). A varied response between immature and adult dogs would likely reflect changes in brain stem maturation. We also attempted to correlate the severity of the cardiovascular response to SP infusion with that of the laryngeal response, but were unable to detect an association.

All animals in this study were breathing spontaneously at the time of SP infusion, but many animals had endured a short period of mechanical ventilation during the surgical preparation period. It is possible that the use of mechanical ventilation may have altered the response of some animals, as mechanical ventilation has been shown to increase the concentration of SP in the vagus nerve.[18]

The laryngeal adductor response to SP infusion was effectively blocked by systemically pretreating the animals with the antagonist CP-96,345. Because this antagonist is specific for the NK-1 tachykinin (SP) receptor, this finding confirmed that the response due to SP infusion is from activation of the NK-1 receptor. The ability to block the laryngeal adductor response by CP-96,345 may have therapeutic implications in preventing laryngospasm and laryngospastic events, a presumed mechanism of apparent life-threatening events and possibly sudden infant death syndrome in pediatric patients.

CONCLUSIONS

1. Peripheral infusion of SP induces a marked increase in electrical activity of the CT and TA adductor muscles of the developing canine larynx. Such a response to systemic infusion of a neurotransmitter has not been previously identified.

2. The magnitude of the laryngeal response to SP infusion varied between animals, but the response occurred in 23 of the 24 studies.

3. The laryngeal response was accompanied by a marked decrease in MAP and an increase in the respiratory rate and depth of respirations.

4. The laryngeal adductor response to SP infusion was blocked by pretreatment of animals with CP-96,345, an SPA specific for the NK-1 tachykinin receptor.

REFERENCES

1. Bauman NM, Sandler AD, Schmidt C, Maher JW, Smith RJH. Reflex laryngospasm induced by stimulation of distal esophageal afferents. Laryngoscope 1994;104:209-14.

2. Bauman NM, Wang D, Jaffe DM, et al. Role of substance P in the laryngeal chemoreflex. Ann Otol Rhinol Laryngol 1998; 107:575-80.

3. Valdes-Dapena M. Crib deaths and focal fibrinoid necrosis of the larynx. J Forensic Sci 1958;3:503-9.

4. Beckwith JB. The sudden infant death syndrome. Curr Probl Pediatr 1973;3:3-36.

5. Valdes-Dapena M. A pathologist's perspective on possible mechanisms in SIDS. Ann N Y Acad Sci 1988;533:31-6.

6. Uddman R, Sundler F. Neuropeptides in the airways: a review. Am Rev Respir Dis 1987;136:S3-S8.

7. von Euler US, Gaddum JH. An unidentified depressor substance in certain tissue extracts. J Physiol (Lond) 1931;72: 74-87.

8. Barber RP, Vaughn JE, Slemmon JR, Salvatera PM, Roberts E, Leeman SE. The origin, distribution and synaptic relationships of substance P axons in rat spinal cords. J Comp Neurol 1979;184:331-51.

9. Culman J, Itoi K, Unger T. Hypothalamic tachykinins, mediators of stress responses? Ann N Y Acad Sci 1995;771:204-18.

10. Bandler R, Carrive P, Shang SP. Integration of somatic and autonomic reactions within the midbrain periaqueductal gray: visceroptic, somatotopic and functional organization. Prog Brain Res 1991;87:269-305.

11. Hsiao D-Y, Solomon NP, Luschei ES, et al. Effect of subglottic pressure on fundamental frequency of the canine larynx with active muscle tensions. Ann Otol Rhinol Laryngol 1994;103:817-21.

12. Larson CR, Yoshida Y, Sessle BJ. Higher level motor and sensory organization. In: Titze IR, ed. Vocal fold physiology. Frontiers in basic science. San Diego, Calif: Singular Publishing Group, 1993:227-75.

13. Hisa Y, Tadaki N, Uno T, Okamura H, Taguchi J, Ibata Y. Neuropeptide participation in canine laryngeal sensory innervation. Immunohistochemistry and retrograde labeling. Ann Otol Rhinol Laryngol 1994;103:767-70.

14. Frigo B, Barbareschi M, Mariscotti C, et al. Substance P–like immunoreactive nerve fibers of the human laryngeal mucosa. Preliminary report. Ital J Neurol Sci 1989;10:69-72.

15. Domeij S, Dahlqvist A, Eriksson A, Forsgren S. Similar distribution of mast cells and substance P– and calcitonin gene–related peptide–immunoreactive nerve fibers in the adult human larynx. Ann Otol Rhinol Laryngol 1996;105:825-31.

16. Wada S, Maeyama T, Watanabe S, Shin T. Substance P immunoreactive nerve fibers of the canine laryngeal mucosa. J Otorhinolaryngol Soc Japan 1987;90:1321-7.

17. Yu YC, Miyazaki J, Shin T. Neuroendocrine cells in the cat laryngeal epithelium. Eur Arch Otorhinolaryngol 1996;253: 287-93.

18. Balzamo E, Joanny P, Steinberg JG, Oliver C, Jammes Y. Mechanical ventilation increases substance P concentration in the vagus, sympathetic, and phrenic nerves. Am J Respir Crit Care Med 1996;153:153-7.

19. Ling EA, Yick TY, Ng GL, Wong WC. Immunocytochemical localisation of substance P in vagal ganglion cells and pericellular arborisations in the monkey. J Anat 1992;181:61-71.

20. Wang LG, Rao ZR, Li HM, Li JS. Prenatal ontogeny of substance P–like immunoreactivity in the nucleus of the vagus nerve of the human fetus: an immunocytochemical study. Brain Res 1993;605:9-17.

21. Arai H, Emson PC. Regional distribution of neuropeptide K and other tachykinins (neurokinin A, neurokinin B and substance P) in rat central nervous system. Brain Res 1986;399: 240-9.

22. Minamino N, Masuda H, Kangawa K, Matsuo H. Regional distribution of neuromedin K and neuromedin L in rat brain and spinal cord. Biochem Biophys Res Commun 1984; 124:731-8.

23. Block CH, Barnes KL, Ferrario CM. The distribution of substance P in the canine dorsomedial medulla. J Cardiovasc Pharmacol 1987;10(suppl 12):S230-S234.

24. Clark JW, Senanayake PD, Solomon GD, Gallagher C. Substance P: correlation of CSF and plasma levels. Headache 1994;34:261-4.

25. Yoshida Y, Miyazaki T, Hirano M, Kanaseki T. Localization of the laryngeal motoneurons in the brainstem and myotopical representation of the motoneurons in the nucleus ambiguus of cats: an HRP study. In: Titze IR, Sherer RC, eds. Vocal fold physiology. Denver, Colo: The Denver Center for the Performing Arts, 1985:74-90.

26. Jean A. Brainstem organization of the swallowing network. Brain Behav Evol 1984;25:109-16.

27. Baude A, Lanoir J, Vernier P, Puizillout JJ. Substance-P in the dorsal medial region of the medulla in the cat: effects of nodosectomy. J Chem Neuroanat 1989;2:67-81.

28. Segu L, Lanoir J, Puizillout JJ. Up-regulation of substance P binding sites in the vagus nerve projection area of the cat brainstem after nodosectomy. A quantitative autoradiographic study. J Chem Neuroanat 1991;4:447-59.

29. Yamada K, Emson P, Kokfelt T. Immunohistochemical mapping of nitric oxide synthase in the rat hypothalamus and colocalization with neuropeptides. J Chem Neuroanat 1996;10: 295-316.

30. Yoshida Y, Miyazaki T, Hirano M, Shin T, Kanaseki T. Arrangement of motoneurons innervating the intrinsic laryngeal muscles of cats as demonstrated by horseradish peroxidase. Acta Otolaryngol (Stockh) 1982;94:329-34.

31. Saleh TM, Cechetto DF. Peptide changes in the parabrachial nucleus following cervical vagal stimulation. J Comp Neurol 1996;366:390-405.

32. Rikard-Bell GC, Tork I, Sullivan C, Scheibner T. Distribution of substance P–like immunoreactive fibres and terminals in the medulla oblongata of the human infant. Neuroscience 1990;34:133-48.

33. Itoi K, Tschope C, Jost N, Lebrun C, Stauss B, Unger T. Identification of the central tachykinin receptor subclass involved in substance P–induced cardiovascular and behavioral responses in conscious rats. Eur J Pharmacol 1992;219:435-44.

34. von Euler US, Pernow B. Neurotropic effects of substance P. Acta Physiol Scand 1956;36:265-75.

35. Helke CJ, Hill KM. Immunohistochemical study of neuropeptides in vagal and glossopharyngeal afferent neurons in the rat. Neuroscience 1988;26:539-51.

Ann Otol Rhinol Laryngol 108:1999

HISTOMORPHOMETRIC AND LARYNGEAL VIDEOSTROBOSCOPIC ANALYSIS OF THE EFFECTS OF CORTICOSTEROIDS ON MICROFLAP HEALING IN THE DOG LARYNX

JOHN R. COLEMAN, JR, MD
SHANE SMITH, MD
LOU REINISCH, PHD
CHERYL R. BILLANTE, PHD
JACOB P. OSSOFF
WALTER DERISO
C. GAELYN GARRETT, MD
NASHVILLE, TENNESSEE

The histologic and functional effects of unilateral, layered corticosteroids on lateral microflap healing in 15 dogs were analyzed. Histologic sections of steroid-treated vocal folds (VFs) were studied with computer morphometry to examine differences in the tissue healing response. Paired analysis revealed increases in the inflammatory infiltrate around the microflap in the steroid-treated VFs at 2, 4, and 6 weeks (6.3%, 30.6%, and 34.9%, all with $p < .02$). The neovascular response in the steroid-treated VFs was less at 2 weeks (–20.9%, $p < .005$) but greater at 4 and 6 weeks (16.3% and 4.3%, $p < .005$). To better characterize the effect of steroids on the healing process, a normal, time-dependent distribution was applied to the histologic data and demonstrated a delay in the steroid-treated VF tissue response of 12 days for the inflammatory infiltrate and 21 days for the neovascular response. Qualitative and quantitative analysis of in vivo laryngeal videostroboscopy (LVS) samples taken preoperatively and at sacrifice could not identify significant differences in appearance, amplitude, mucosal wave, or suppleness between the 2 VFs. Therefore, although corticosteroids cause a delay in wound healing, LVS does not discern differences in microflap characteristics between healing steroid-treated and control VFs at 2, 4, or 6 weeks. If steroids are used, the surgeon should account for a probable delay in wound healing, but should not expect an overall difference in functional outcome.

KEY WORDS — corticosteroids, microflap, vocal cord, vocal fold, wound healing.

INTRODUCTION

Over the last several years, microsurgery on the larynx has concentrated on the removal of benign disease with preservation of the surrounding normal tissue. The lateral microflap and the medial microflap are the most prominent techniques implemented for this practice.[1-3] These procedures are based on the histology of the human vocal fold and on the histopathology of most benign vocal fold lesions.[4,5] By operating within the superficial layer of the lamina propria, the diseased tissue can be removed while the normal mucosa and the underlying vocal ligament are preserved. This technique normally results in minimal scarring and improved wound healing. The lateral microflap is specifically designed to lift the mucosal cover along the surface of the vocal fold, remove the pathologic tissue, and then redrape the remaining mucosal cover. The technique is effective, with subjective and objective improvement in vocal fold closure and return of the mucosal wave.[1]

The mucosal wave is generated by the sliding of the mucosal cover over the vocal ligament and vocalis muscle. Scarring can cause fixation of the mucosal cover to the deeper tissues, thus perturbing the mucosal wave. Research and clinical experience demonstrate that fixation of the mucosal cover to the deeper tissues impairs the quality of the voice following vocal fold surgery. In experimentation on cats, repeated strippings of the vocal fold mucosa resulted in an increase in the fibrous tissue of the vocal fold.[6] The increase in fibrous tissue limits the movement of the mucosal cover, distorts the relationship of the cover to the body, and creates dysphonia. Clinically, Woo et al[7] found vocal fold scarring to be the most common cause (35%) of dysphonia following laryngeal surgery.

As an adjunct to microflap surgery, steroids have been used clinically in laryngeal surgery in an attempt to reduce scarring. Bouchayer and Cornut[8] reported on the use of steroids in the treatment of iatro-

---

From the Department of Otolaryngology, Vanderbilt Bill Wilkerson Center for Otolaryngology and Communication Sciences at the Vanderbilt University Medical Center, Nashville, Tennessee. This work was supported in part by a grant for the Medical Free Electron Laser Project, administrated by the Office of Naval Research under grant number N00014-94-11023. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Vanderbilt University.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 11-12, 1998. Awarded first place in the Resident Research Competition.

CORRESPONDENCE — C. Gaelyn Garrett, MD, Dept of Otolaryngology–Head and Neck Surgery, S-2100 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232-2559.

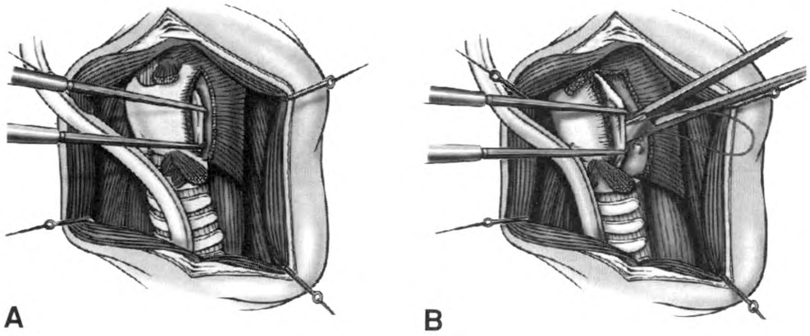


Fig 1. Illustration demonstrates our approach to laryngeal videostroboscopy in dogs. A) Thyrohyoid and inferior constrictor muscles have been divided; thyroid ala is being rotated with single-prong hooks. Next step involves dissection of pyriform sinus off thyroid cartilage to expose muscular process of arytenoid. B) Nylon suture (3-0) has been secured to muscular process, and suture is being passed through paraglottic space.

genic scarring of the vocal fold. They injected steroids into the vocal fold and then elevated a microflap. After redraping the mucosa, they halted the procedure and allowed the fold to heal. They reported improvement in vocal fold suppleness, in vocal fold closure, and in voice quality. Courey et al[1] also described the use of steroids under the microflap after the excision of benign lesions. Steroids were used to theoretically reduce scarring following the microflap.

Since scarring of the lamina propria causes postoperative dysphonia, any technique, medication, or change in preoperative or postoperative care that reduces scar formation during the healing phase is beneficial to improving the results of laryngeal microsurgery. This study is an analysis of the effect of steroids on lateral microflap healing in the dog larynx. Results are analyzed objectively via computer morphometry of histologic sections of the healing fold, and subjectively and objectively with laryngeal videostroboscopy (LVS).

MATERIALS AND METHODS

All procedures and actions were approved and monitored by the University Animal Care Committee. Experimentation was performed on 16 mongrel dogs. Each animal underwent general anesthesia with Pentothal induction and maintenance with halothane inhalation agent delivered via a cone mask or tracheotomy tube. They received preoperative, intraoperative, and postoperative antibiotics (penicillin G procaine, penicillin G benzathine, and gentamicin sulfate). Postoperative pain control was with flunixin meglumine. Finally, intraoperative monitoring consisted of an electrocardiogram and measurements of the depth and quantity of spontaneous respiration and the level of pain threshold.

At the original surgery, all animals underwent neck exploration in preparation for LVS.[9,10] A vertical incision was made in the midline. The strap muscles were identified and separated laterally. The laryngotracheal apparatus was identified and cleaned of fascial debris. On each side, the thyrohyoid and inferior constrictor muscles were identified and divided. The thyroid ala was rotated with 2 single-prong hooks (Fig 1A). With the posterior border of the cartilage exposed, a sharp elevator was used to separate the pyriform sinus mucosa from the inner perichondrium of the thyroid ala. With palpation, the muscular process of the arytenoid cartilage was identified. A 3-0 nylon suture was passed through the muscular process and tied securely. The suture was then passed through the paraglottic space and through the anterior portion of the thyroid ala (Fig 1B). Two separate tracheotomies were performed. The lower tracheotomy provided a conduit for the inhalation agent, while the superior tracheotomy allowed for the introduction of tubing from the air compressor. The air from the compressor (pressure was regulated at the compressor) was passed through a heated humidifier and a needle valve. The compressor was set at a constant pressure for all the stroboscopic examinations.[11] The needle valve (located just before the tubing passed through the superior tracheotomy) was opened until the vocal folds started to vibrate. The valve was then held constant for the stroboscopic examination. The column of air was delivered to the subglottic region to provide airflow through the adducted true vocal folds.

In order to acquire the LVS images, traction was applied to the arytenoid adduction sutures while airflow was delivered via the subglottic tubing (Fig 2). The LVS equipment included a Panasonic SVHS recorder (model AG-7350, Matsushita Communication Industrial Co, Ltd, Japan), a microchip camera (model IK-C40A, Toshiba Corporation, Japan), and a Bruel and Kjaer stroboscope (type 4914, Denmark).

Once adequate data were acquired, the animal was prepared for endoscopic laryngeal surgery. Exposure of the dog larynx was performed with a modified Ossoff-Karlen laryngoscope (Pilling, Fort Washington, Pa); magnification was obtained with a Zeiss operating microscope (model OPMI-DFC, Carl Zeiss, Inc, Thornwood, Pa) with a 400-mm lens; and laryngeal dissection was performed with the Feder-Ossoff laryngeal instruments (Pilling No. 50-6890).

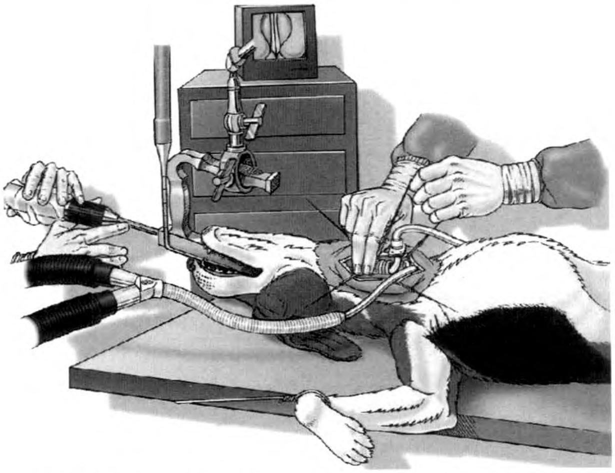


Fig 2. Drawing shows overall setup for laryngeal videostroboscopy in dog model. Sterile drapes are omitted for illustrative purposes.

Bilateral, symmetric lateral microflaps were created by surgeons with extensive experience with clinical microflap surgery. The incisions started at the level of the vocal process of the arytenoid and continued anteriorly to within 3 mm of the anterior commissure; the elevation of the microflap medially extended 3 mm beyond the free edge of the vocal fold. On one side, which routinely varied, 1 mL of triamcinolone acetonide was layered under the microflap as described by Courey et al.[1]

The inhalation route was then changed to a cone mask, and the neck was closed in layers. Two-layer closure of the tracheotomy sites with 3-0 chromic suture around the rings and 3-0 Vicryl suture in a perichondrium layer ensured the prevention of tracheocutaneous fistula.

At each interval of 2, 4, or 6 weeks, 5 of the 15 total dogs were returned to the operating room and LVS was again performed in a fashion analogous to the above-noted procedure, using the previously placed arytenoid sutures. The animals were then painlessly sacrificed with a lethal dose of a barbiturate; their larynges were harvested and placed in 10% formalin for several days prior to sectioning. Preparation of the blocks for histologic processing was performed in the departmental laboratory; the vocal fold was divided in the coronal plane at the midfold level. This ensured that the histologic samples analyzed were from the same section of the vocal fold and occurred in the region of the vibratory segment. The samples were taken to the Division of Histopathology for processing.

HISTOLOGY

Specimens were decalcified, sectioned by a rotary microtome (4 to 5 μm), and stained by standard techniques. Staining techniques were hematoxylin and eosin and Movat's[12] modification of the pentagastrin stain. Samples were prepared at different time intervals. In order to aid in the standardization, a senior technician performed the staining process; control slides were employed to maintain color quality. The Movat's stain highlights elastin, immature collagen, and mature collagen; this technique provided enhanced localization of the neovascularity. The hematoxylin and eosin stain was used to analyze the inflammatory infiltrate surrounding the microflap region.

The histologic analysis was quantified with the Zeiss microscope system (model 4521-85) and ImagePro Version 1.0 (Carl Zeiss, Inc). A 200× magnification was used to study the region of the microflap. Individual images demonstrating the microflap were captured, and computer morphometric analysis was performed. This portion of the analysis was performed in a blinded fashion with extensive oversight of the computer morphometric analysis to ensure consistency. Using digital enhancement and magnification, the color range specific to the inflammatory cells in the hematoxylin and eosin preparation and the blood vessels in the Movat's stain were selected for each batch of slides. The program using the specific color pixels previously identified was then asked to identify the number of samples (inflammatory cells or blood vessels) that contained the same histologic staining within an area surrounding the region of the microflap and specified by the computer operator. Similarly, the program calculated the area within the specified field, allowing for a number of inflammatory cells or blood vessels per unit area (a number density) to be calculated. Five to seven fields of each stain were analyzed per vocal fold per dog; these numbers were averaged to obtain a value for each dog vocal fold. The averages of the steroid and control sides were then compared by calculating the percent difference between the values obtained at 2, 4, and 6 weeks. Our comparison was defined so that a negative value would represent an effective decrease in the inflammatory infiltrate or the neovascular response for that time point in the steroid-treated vocal fold.

MODEL FOR HISTOLOGIC RESPONSE

In an effort to better understand the time response and the overall effect of the steroids on the time response of the inflammatory infiltrate and the neovascular response, we applied a normal, time-dependent distribution to the morphometrically determined number densities obtained at 2, 4, and 6 weeks. A normal gaussian distribution model was chosen because it represented a simple model with only 3 variables. It provided for a smooth onset of action and a smooth termination of the response. Although the simple model that we created could not account for all the intricacy of the complex healing process, it did adequately describe the data, allowing the application of a linear least-squares fit to determine the best parameters for the data.

This time response can be written as

$$F(t) = A\exp[-(t - t_{peak})^2/s^2]$$

where F(t) represented the number density of cells or vessels. The 3 variables identified in this simple model were the time point for the peak of the response (t_{peak}), the maximum amplitude of the response or number density (A), and the duration of the response (s). We then used a linear least-squares fit to determine the best values for each variable to describe the measured data. The data were consistent, with 2 of the variables held constant (A and s) and the steroids only affecting the time point for the peak of the inflammatory infiltrate and the neovascular responses when compared to the control vocal fold.

LARYNGEAL VIDEOSTROBOSCOPIC ANALYSIS

Qualitative. All LVS samples obtained were condensed with a video editor into a single tape of 1-minute samples. The samples were assigned a number so that evaluators would have no knowledge of the subject number, under which side the steroid was placed, or whether the sample was preoperative or postoperative. Evaluators were told that each pair of samples (ie, numbers 1 and 2) did represent the same animal. Five speech and language pathologists, all trained in the acquisition and interpretation of human LVS, evaluated the 30 samples and described on a standardized form the anatomy (edema, hemorrhage, and inflammation) and the LVS analysis (symmetry, amplitude, and mucosal wave). The anatomic descriptions were based on the vocal fold (right or left), the anterior to posterior one-third location on the vocal fold, the vertical position on the vocal fold (upper lip, lower lip, or glottic surface), and the amount noted (small, moderate, or large). In the stroboscopic analysis the symmetry was deemed normal, side to side, teeter-totter, or unequal vertical phase; while the amplitude was graded as equal, R>L, L>R, or both decreased. The mucosal wave analysis examined each fold individually and rated the wave as normal, great, decreased, abnormal pattern, or adynamic or absent. Their subjective analyses were then collated to produce trends. In the analysis of the anatomic characteristics, we compared the appearances of the steroid fold preoperatively and postoperatively, the control fold preoperatively and postoperatively, and the steroid fold versus the control fold postoperatively. We compared the stroboscopic appearance of the preoperative steroid-treated vocal fold to that of the postoperative steroid-treated vocal fold, using the nontreated vocal fold as an internal control.

Quantitative. We have previously analyzed multiple videostroboscopic samples of patients with unilateral, stiff, adynamic vocal folds. One trend noted was that when the lower lips were closed during LVS immediately following the "glottal puff," there was a substantial difference in the excursion of the upper lip of the normal vocal fold compared to the damaged fold.[9] We believe that the extent of the upper lip excursion of the vocal fold at lower lip closure is related to the suppleness of the tissue. Woo et al[13] have speculated that the vocal fold postsurgery must be "soft, pliable and supple" in order to effectively modulate airflow. The extent of scarring in the lamina propria of the vocal fold can then limit the suppleness of the tissue and the effectiveness of the fold in voice production.

We quantified the extent of upper lip excursion following the "glottal puff" at lower lip closure, capturing individual video frames off a Panasonic SVHS player into a Macintosh computer (660 AV, Cupertino, Calif) using the built-in video port. Measurements were made with Adobe Photoshop 4.0 (Mountain View, Calif). The center of closure was identified, and a line from the anterior to the posterior commissure was drawn. Distances were measured perpendicular to this line to the point of greatest lateral excursion. Five frames from different cycles of each preoperative and postoperative video sample were acquired and analyzed by the first and sixth authors to ensure consistency. We took the distance of maximum excursion of the steroid-treated vocal fold and divided it by the distance of the control vocal fold for each frame. We then averaged the 5 frames and subtracted the preoperative value from the postoperative value. The preoperative ratio was subtracted from the postoperative ratio to compensate for any inherent asymmetry of the individual animals. A positive value would represent greater "suppleness" to the steroid side and thus presumedly less scarring.

STATISTICAL ANALYSIS

All data were analyzed with StatView (Abacus Concepts, Berkeley, Calif). Differences were evaluated with a 2-tailed Student's *t*-test using a paired comparison. Statistical significance was defined as a $p < .05$. Intrareviewer and interreviewer variations were determined from the mean squared value of the scoring (0 is normal and 1 is abnormal). These values were analyzed independently before and after micro-

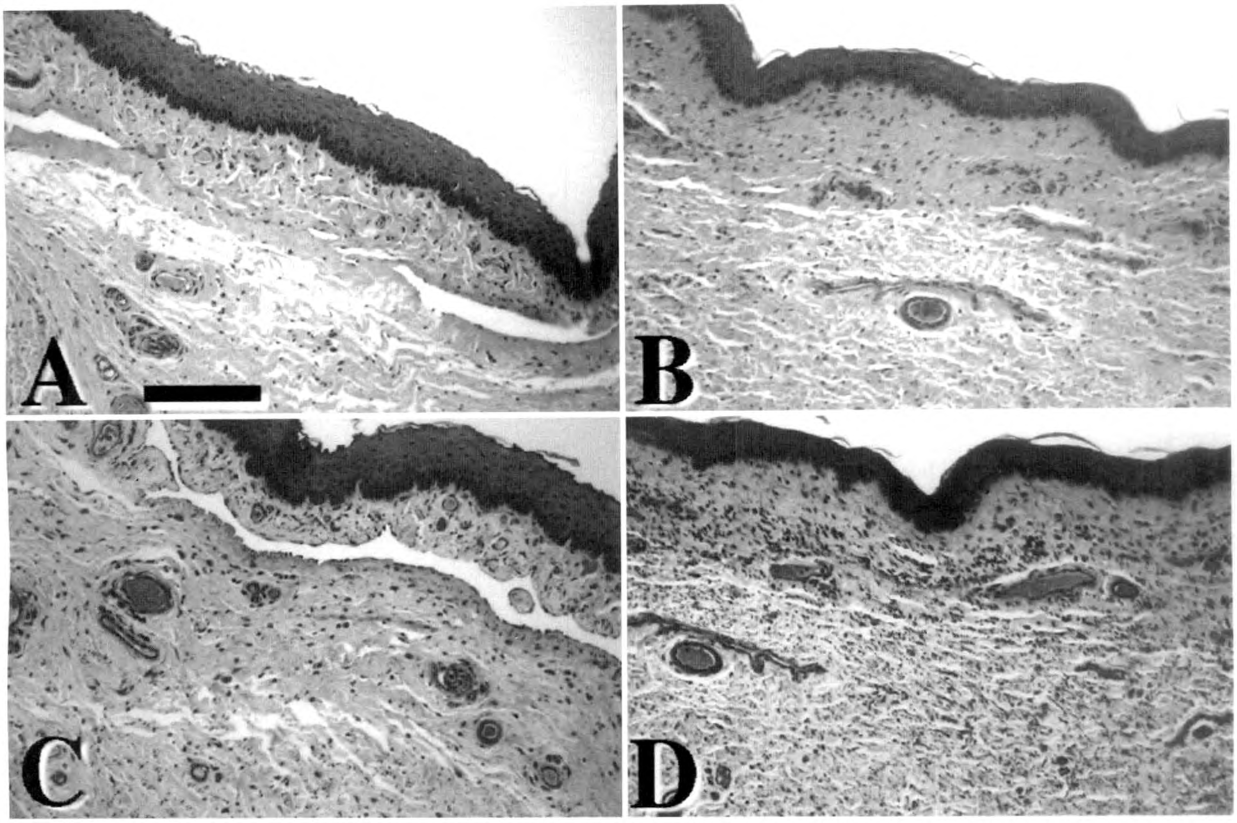


Fig 3. Photomicrographs depict coronal histologic sections as used for morphometric analysis (original ×200). All sections are from same dog, who was painlessly sacrificed at 6 weeks. Steroid was layered under left vocal fold in this animal. Bar in A — 100 µm. A) Left vocal fold (H & E). B) Right vocal fold (H & E). C) Left vocal fold (Movat's stain). D) Right vocal fold (Movat's stain).

flap surgery and analyzed with an ANOVA, repeated measurement F-test.

RESULTS

Sixteen dogs underwent the initial neck exploration for the purpose of videostroboscopy; 1 animal did not have palpable muscular processes of the arytenoid cartilages, which are needed for the placement of adduction stitches. This animal was reassigned to an alternative project, as LVS could not be performed by our technique. The remaining 15 dogs successfully underwent videostroboscopy preoperatively and at sacrifice and microlaryngeal surgery. The animals were divided into 3 equal groups of 5 for sacrifice at 2, 4, and 6 weeks.

Complications encountered during the procedure included 2 animals that required an additional operation to perform LVS because edema at the time of the original neck exploration prevented an adequate mucosal wave. Three animals developed neck seromas that required drainage and additional antibiotic therapy, and 1 dog had a tracheocutaneous fistula that required an additional operation for closure. No animal experienced respiratory compromise during the experiment.

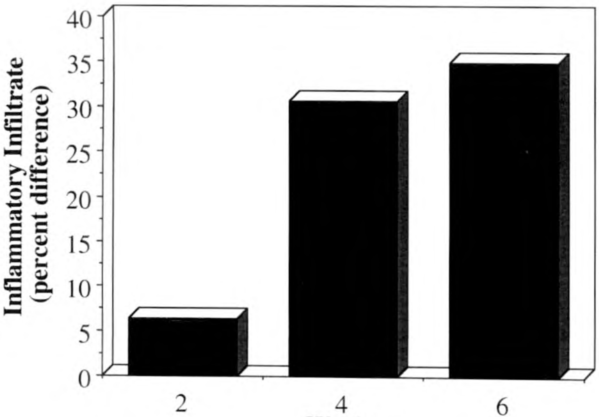


Fig 4. Histogram details percent increase in inflammatory infiltrate at 2, 4, and 6 weeks in steroid-treated vocal folds as compared to control vocal folds.

HISTOLOGY

Five representative sections on the hematoxylin and eosin–stained slides were obtained for each vocal fold of each dog (Fig 3A,B). Calculations of the average number density and then comparison of the values obtained for the control and steroid vocal folds revealed statistically significant increases in the inflammatory infiltrate around the steroid-treated vocal fold. At 2 weeks the percent difference was 6.3%

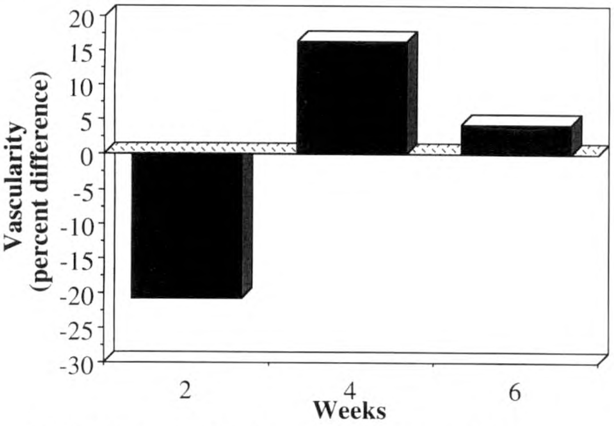


Fig 5. Histogram details percent decrease and increase in neovascular response at 2, 4, and 6 weeks in steroid-treated vocal folds as compared to control vocal folds.

(p = .016); this difference increased to 30.6% (p = .003) at 4 weeks and 34.9% (p = .004) at 6 weeks (Fig 4).

Seven representative sections were obtained for each fold in the Movat's staining (Fig 3C,D). Once again, the analysis was designed so that a negative value represented an effective decrease in the neovascular response in the steroid vocal fold. At 2 weeks the steroid fold had 20.9% less vascularity than the untreated vocal fold (p = .002). However, at 4 weeks the steroid-treated vocal fold demonstrated 16.3% more vascularity than the control fold (p = .001), and at 6 weeks the percent difference represented a small but statistically significant increase (4.3%, p = .005; Fig 5).

MODEL OF HISTOLOGIC RESPONSE

We considered the values from the steroid-treated side and the untreated control side separately in this analysis. A linear least-squares fit technique was used to define the best parameters for the response time.

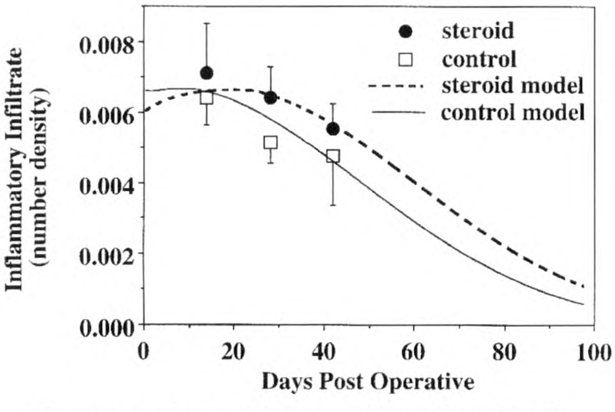


Fig 6. Graph demonstrates normal, time-dependent distribution model that conforms to our morphometric histology analysis. It shows number density of inflammatory infiltrate over time for steroid-treated and control vocal folds. Layered steroid delays peak response by 12 days.

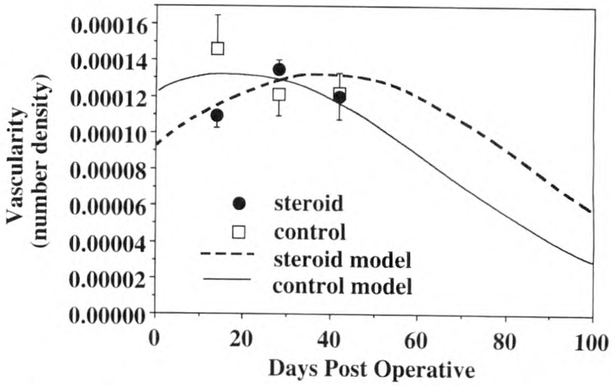


Fig 7. Graph depicts number density of neovascular response over time for steroid-treated and control vocal folds. Steroid delays peak neovascular response by 21 days.

We determined that we could accurately describe the data by holding the maximum number density (A) of the normal distribution to 0.0066 for the inflammatory infiltrate and 0.00013 for the neovascularization. We could also fix the duration of the response (s) at 58 days for the inflammatory infiltrate and at 66 days for the neovascularization. Using these values, we described the effect of the steroids to be a change in the peak response time (tpeak) for these processes in the wound healing (Figs 6 and 7). We found that a delay in the response of the tissue on the steroid-treated side occurred, with the inflammatory infiltrate data consistent with a delay of 12 days and the neovascularization data consistent with a delay in tissue response of 21 days. This model demonstrated a time delay due to the steroid, but no overall change in the amount of the response.

LARYNGEAL VIDEOSTROBOSCOPIC ANALYSIS

Qualitative. Responses from our speech and language pathologists were collated within a spreadsheet and analyzed on the basis of anatomic characteristics (edema, hemorrhage, and inflammation) and LVS findings (symmetry, amplitude, and mucosal

QUALITATIVE LARYNGEAL VIDEOSTROBOSCOPIC ANALYSIS

	Weeks	*Steroid Post/Pre > Control Post/Pre*	*Steroid Post/Pre = Control Post/Pre*	*Steroid Post/Pre < Control Post/Pre*
Amplitude	6	0	5	0
	4	1	3	1
	2	2	2	1
	Total	3	10	2
Mucosal wave	6	2	2	1
	4	1	4	0
	2	1	2	2
	Total	4	8	3

Data are numbers of dogs.

wave). Such comparisons were made preoperatively and at 2, 4, and 6 weeks.

In each of the groupings of the anatomic data, no documented, statistically significant differences could be identified. An example of the symmetry of the data is that overall, 7 dogs were found to have a steroid-layered vocal fold with the same appearance as the control vocal fold postoperatively, 7 dogs had a steroid fold with a slightly worse appearance, and 1 had a steroid fold with a slightly better appearance.

The stroboscopic data also demonstrated few differences between the steroid side and the control side (see Table). Overall, 14 dogs were found to have equal symmetry preoperatively versus postoperatively. In comparison of vocal folds, the amplitude of the steroid-treated fold was equal to that of the control fold in 10 dogs, greater than that of the control in 3 dogs, and less than that of the control in 2 dogs. The mucosal wave data also demonstrated remarkable symmetry, with 8 dogs having an equal mucosal wave, 4 dogs having a greater mucosal wave in the steroid fold, and 3 dogs having a greater mucosal wave in the control fold.

As a validation of the scores from the independent speech pathologists, the intrareviewer and interreviewer variances were examined. The pre– and post–microflap incision stroboscopic data were separated for this analysis. Normal and abnormal assessments were designated with a 0 and a 1, respectively. With an ANOVA for repeated measurements, the interreviewer and intrareviewer variation was determined with paired comparisons. For the preoperative data, the intrareviewer mean square score was 0.31 and the interreviewer mean square score was 2.40. For the postoperative data, the intrareviewer mean square score was 0.26 and the interreviewer mean square score was 1.15. The overall F-test value was 2.34. This is within the $F(95\%) \leq 8.53$ for the sample size and the multiple reviewers. Thus, the evaluations were consistent for each review and between the reviewers.

Quantitative. The evaluation of the difference of upper lip excursion when the lower lips were in contact was performed such that a positive value would imply that the excursion of the steroid fold divided by that of the control fold postoperatively was greater than it was preoperatively. This would imply more "suppleness" to the vocal fold with steroid under the microflap and portend less scarring during the healing process.

At 2 weeks the percent difference of the postoperative-minus-preoperative excursion ratio was –9.2% ($p = .15$). At 4 weeks the value was 4% ($p = .53$) and it was –5.2% at 6 weeks ($p = .44$). Overall, the difference was –3.5% ($p = .32$). There are no measurable differences in these data.

DISCUSSION

Scar formation within the layers of the lamina propria of the vocal fold results in an abnormal relationship of the cover to the body. The perturbation causes poor sliding of the cover, creating a decrease in the mucosal wave, and as scarring worsens, adynamic segments can develop along the vocal fold. The inability or the decreased ability to vibrate the vocal fold creates the dysphonia that we associate with scarring. Corticosteroids are often used in conjunction with the microflap in an attempt to prevent scar formation and ensure a better-quality voice. Systemic steroids are known to delay wound healing. However, the effect of local steroids on voice quality has not been studied quantitatively. In this experiment we sought to determine if corticosteroids layered under a lateral microflap would lead to a reduction in scar formation and thus improve results of microlaryngeal surgery. The experiment was designed in the dog model, with no postoperative "voice rest." No animal model completely parallels the histology of the human vocal fold.[14] The dog model has frequently been used for laryngeal research despite the differences in the lamina propria as compared to the human vocal fold. The dog vocal fold has a 2-layer lamina propria, with the superficial layer having a high concentration of elastin and collagen fibers and the deeper layer having less concentration of elastin and collagen. The deeper layer resembles the loose connective and areolar tissue of the superficial lamina propria of the human. The microflap in the dog is found in the deeper layer of the lamina propria, so that the histologic region of the microflap is analogous in the dog and the human.[10] Moreover, the ease and accuracy with which LVS can be performed in the dog make this animal model a good choice for this analysis, as both histologic and functional analyses of the results can be performed.

Wound healing is characterized by 3 temporal processes: the inflammatory phase, the proliferative phase, and the remodeling phase.[15] Fibroblasts, neutrophils, macrophages, and plasma cells constitute the majority of the acute and chronic inflammatory cells seen during the 3 phases of wound healing. These cells arrive via existing and neovascular channels and release angiogenesis factors that contribute to additional blood supply. The inflammatory infiltrate then accounts for the deposition and reabsorption of fibrin and collagen below the epithelium. The distribution, quality, and quantity of the fibrin and collagen can lead to differences in tissue healing.

Histomorphometric analysis was performed to evaluate the healing pattern over time of the dog vocal folds. This demonstrated statistically significant differences in the inflammatory infiltrate and the neovascular response at 2, 4, and 6 weeks when comparing the steroid-treated to the untreated control vocal folds. Percent increases and decreases could be interpreted as overall increases or decreases in response, a change in the duration of the response, or a delay or acceleration of the response. To attempt to understand the response itself and the time course of the response, we chose a normal, time-dependent distribution and a linear least-squares analysis. The chosen model was simple, and the data were most consistent when the duration of the response and the maximum amplitude of the response were held constant. Wound healing is complex and multivariable. There may also be subtle changes that were not discerned in the maximum amplitude and the duration of the response. Further, the model has not been validated, and therefore, the analysis can only suggest an interpretation of a time delay in the healing process. We find this interpretation helpful in understanding the statistically significant measured differences.

Our data show that the inflammatory response starts almost immediately and has a duration of approximately 58 days (Fig 6). The peak of response is at 6 days for the control vocal fold and delayed to 18 days for the steroid-treated vocal fold. Moreover, the proliferative phase of wound healing is normally accompanied by an increase in vascularity. We observed this increase in the morphometry of the histologic slides (Fig 7). In the control vocal fold the vascularity had a peak response at 18 days, with a duration of 66 days. In the steroid-treated vocal fold, the response was similar but delayed to a peak of 39 days. In this model the steroid caused a delay in the tissue response time compared to the controls. The clinical importance of this delay in wound healing could be significant, especially if the surgeon uses voice rest following laryngeal surgery. If steroids are layered under the microflap, the surgeon should consider the delay caused by the steroids when prescribing the duration of the voice rest.

We used LVS to determine if the steroids caused any changes in the physiology or anatomy of the vocal folds that could affect the potential outcome of voice results. Laryngeal videostroboscopy is uniquely qualified to measure subtle changes by characterizing the dynamic motion of the vibratory margin of the vocal fold. Anatomic and physiologic measures include closure, periodicity, and mucosal wave. The information provides an indirect measure of the condition of the vocal fold. Submucosal masses and processes, including scarring, can be assessed by the distortion created in the glottic cycle. Documented findings associated with scarring in humans include asymmetric amplitude, decreased to absent mucosal wave, incomplete closure, and a nonvibratory segment.[16] Moreover, the videostroboscopic characteristic associated with improved vocal function in the postsurgical state is restoration of the amplitude, mucosal wave, and vocal fold edge.[13]

In the dog, LVS allows for both qualitative and quantitative measures of variables associated with microflap healing. Speech and language pathologists evaluating the LVS samples of the dogs could not discern anatomic or stroboscopic differences between the steroid-layered vocal fold and the control vocal fold at 2, 4, or 6 weeks. Specifically, the mucosal wave was equal between the steroid-treated and the untreated vocal folds in 8 dogs and nearly equally divided between greater and lesser than in the remaining dogs; the amplitude of the vocal folds when compared was equal in two thirds of our sample (see Table). Quantitatively, LVS allows for comparison of the "suppleness" of the vocal folds. At each time point, no statistically significant difference between the steroid-layered and control vocal folds could be documented. Therefore, LVS could not discern a functional difference as a result of a delay in healing between the two vocal folds.

SUMMARY

Steroids layered under the lateral microflap cause a shift in tissue response and a delay in wound healing. We have modeled the response of the inflammatory infiltrate and neovascularization during healing to reveal these delays. Yet, no discernible differences in microflap healing can be documented with LVS. Assuming these results are also valid in humans, the surgeon must anticipate and account for the delay in healing if steroids are used and expect no significant improvement or worsening of vocal fold characteristics and function.

ACKNOWLEDGMENTS — The authors thank Kimberly A. Chachere, MS, Dominic Doyle, MA, Molly Erickson, PhD, Jackie L. Gartner, MA, Paul Gross, MS, CMI, Shan Huang, MD, Melissa Portell, MS, and Mike Slowey, MS.

REFERENCES

1. Courey MS, Gardner GM, Stone RE, Ossoff RH. Endoscopic vocal fold microflap: a three-year experience. Ann Otol Rhinol Laryngol 1995;104:267-73.

2. Sataloff RT, Spiegel JR, Heuer RJ, et al. Laryngeal mini-microflap: a new technique and reassessment of the microflap saga. J Voice 1995;9:198-204.

3. Courey MS, Garrett CG, Ossoff RH. Medial microflap for excision of benign vocal fold lesions. Laryngoscope 1997;107:340-4.

4. Hirano M. Surgical anatomy and physiology of the vocal fold. In: Gould WJ, Sataloff RT, Spiegel JR, eds. Voice surgery. Chicago, Ill: Mosby–Year Book, 1993:125-58.

5. Courey MS, Shohet JA, Scott MA, Ossoff RH. Immunohistochemical characterization of benign laryngeal lesions. Ann Otol Rhinol Laryngol 1996;105:525-31.

6. Leonard RJ, Kiener D, Charpied G, Kelly A. Effects of repeated stripping on vocal fold mucosa in cats. Ann Otol Rhinol Laryngol 1985;94:258-62.

7. Woo P, Casper J, Colton R, Brewer D. Diagnosis and treatment of persistent dysphonia after laryngeal surgery: a retrospective analysis of 62 patients. Laryngoscope 1994;104:1084-91.

8. Bouchayer M, Cornut G. Microsurgery for benign lesions of the vocal folds. Ear Nose Throat J 1988;67:446-66.

9. Moore DM, Berke GS, Hanson DG, Ward PH. Videostroboscopy of the canine larynx: the effect of asymmetric tension. Laryngoscope 1987;97:543-53.

10. Garrett CG, Coleman JR, Courey MS, Reinisch L, Ossoff RH. Comparative histology and vibration of the vocal folds: implications for experimental studies in laryngeal microflap surgery. Otolaryngol Head Neck Surg 1997;117:100-1.

11. Nasri S, Namazie A, Ye M, Kreiman J, Gerratt BR, Berke GS. Characteristics of an in vivo canine model of phonation with a constant air pressure source. Laryngoscope 1996;106:745-51.

12. Movat HZ. Demonstration of all connective tissue elements in a single section. Arch Pathol 1955;60:289-95.

13. Woo P, Casper J, Colton R, Brewer D. Aerodynamic and stroboscopic findings before and after microlaryngeal phonosurgery. J Voice 1994;8:186-94.

14. Kurita S, Nagata K, Hirano M. A comparative study of the layer structure of the vocal fold. In: Bless DM, Abbs JH, eds. Vocal fold physiology. Contemporary research and clinical issues. San Diego, Calif: College-Hill Press, 1983:3-21.

15. Gibson FB, Perkins SW. Dynamics of wound healing. In: Bailey BJ, ed. Head and neck surgery–otolaryngology. Philadelphia, Pa: JB Lippincott, 1993:187-98.

16. Benninger MS, Alessi D, Archer S, et al. Vocal fold scarring: current concept and management. Otolaryngol Head Neck Surg 1996;115:474-82.

≈

FIFTH INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Fifth International Conference on Head and Neck Cancer will be held July 29–August 2, 2000, in San Francisco, California. For information, contact Concepts in Meetings & Events, Robin L. Wagner, President, 7819 Lloyd Ave, Pittsburgh, PA 15218-1941; telephone (412) 243-5156; fax (412) 243-5160; e-mail rlwa@med.pitt.edu.

Ann Otol Rhinol Laryngol 108:1999

RADIOTHERAPY FOLLOWED BY NECK DISSECTION FOR SMALL HEAD AND NECK CANCERS WITH ADVANCED CERVICAL METASTASES

STEVEN J. WANG, MD
MARILENE B. WANG, MD
THOMAS C. CALCATERRA, MD
LOS ANGELES, CALIFORNIA

Patients with small or occult primary carcinomas of the head and neck with advanced cervical metastases present a difficult problem for the otolaryngologist. A retrospective review was performed of patients who presented to UCLA Medical Center between January 1986 and June 1996 with small or occult primary tumors of the head and neck with advanced cervical metastases. The treatment algorithm consisted of initial radiotherapy to the primary site and the neck, followed in 6 to 8 weeks with endoscopy and biopsy of the primary tumor site. As long as the repeat biopsy of the primary tumor site was negative by frozen section, an immediate neck dissection was performed, even if no residual neck disease was present. Almost 40% of patients with no clinical evidence of neck disease following radiotherapy had evidence of metastatic cancer on histopathologic examination. While some would consider a watchful waiting policy when there is no clinically detectable neck disease following radiotherapy, we believe it is preferable to perform immediate surgery in such patients, in light of the high incidence of microscopic metastatic disease.

KEY WORDS — head and neck cancer, neck dissection, radiotherapy.

INTRODUCTION

Patients who present with advanced cervical metastases arising from small or occult primary carcinomas of the head and neck present a difficult problem for the otolaryngologist. Although the primary site can usually be treated satisfactorily with radiotherapy alone, combined surgery and radiotherapy to the neck is often required to obtain tumor eradication. The question then arises as to whether the patient should undergo radiotherapy to the primary site and neck followed by surgery on the neck, or whether neck dissection should precede the radiotherapy. While there remains no consensus on this issue, we believe there are distinct advantages to administering radiotherapy prior to performing neck dissection.

Our treatment algorithm consists of initial radiotherapy to the primary site and neck, followed in approximately 6 to 8 weeks with repeat endoscopy and biopsy of the primary tumor site. As long as the repeat biopsy of the primary site is negative by frozen section, we proceed with an immediate neck dissection. In cases in which there is residual palpable adenopathy following radiotherapy, the need for surgery is clear. Less clear, however, is the need for surgery when a complete clinical response to radiotherapy is achieved in the neck. Some would argue that such patients could be carefully observed — with surgery reserved for later documented recurrence.[1] However, it has been our policy to perform a planned neck dissection even when there is no clinically detectable residual neck disease. We believe that the incidence of microscopic metastases in patients with a clinically negative neck examination following radiotherapy warrants a neck dissection and that a neck dissection diminishes the possibility of subsequent unresectable recurrent disease. We present a series of 26 patients who presented with small or occult primary tumors of the head and neck with advanced neck metastases who were treated with this strategy over the past 10 years.

PATIENTS AND METHODS

Between January 1986 and June 1996, 26 patients who presented with small or occult primary squamous cell carcinomas of the head and neck with advanced cervical metastases (>3 cm or multiple nodes) were treated with initial radiotherapy to the primary site and neck followed approximately 6 to 8 weeks later with a repeat endoscopy and biopsy of the primary site, if known. As long as the repeat biopsies of the primary site were negative by frozen section, an immediate neck dissection was carried out. Small primary tumors were defined as T1, T2, or superfi-

---

From the Division of Head and Neck Surgery, Department of Surgery, University of California at Los Angeles School of Medicine, Los Angeles, California.

Presented at the meeting of the American Society for Head and Neck Surgery, Scottsdale, Arizona, May 13, 1997.

CORRESPONDENCE — Marilene B. Wang, MD, Division of Head and Neck Surgery, UCLA Medical Center, CHS 62-132, 10833 LeConte Ave, Los Angeles, CA 90095.

TABLE 1. RELATIONSHIP BETWEEN T AND N STAGES

	N2a	*N2b*	*N2c*	*N3*	*Nx*
Tis	0	0	0	0	1
T1	8	2	1	1	3
T2	2	0	0	2	0
T3	2	0	0	0	0
T4	0	0	0	0	0
Tx	2	0	0	2	0

Data are numbers of patients (N = 26).

cial T3. Sixteen patients were men, and 10 patients were women. The mean age of the group was 57 years (range 34 to 77 years).

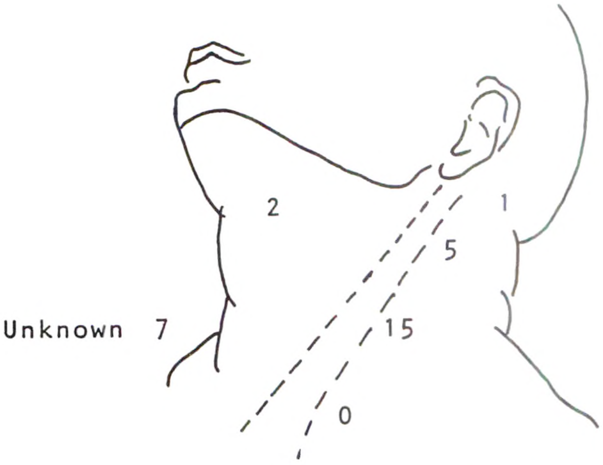
Table 1 shows the relationship between T and N stages. Patients with unknown primary tumors were staged Tx. In several cases, patients presented following an incisional neck biopsy done at an outside hospital, making accurate assessment of the neck disease difficult. These patients were staged Nx. All patients were evaluated by endoscopy, computed tomography (CT), or magnetic resonance imaging (MRI). Although all the neck dissections were performed at our institution, the majority of patients had their radiotherapy completed at outside institutions. The average length of time between completion of radiotherapy and neck dissection was 54.9 days (range 20 to 150 days). In 2 cases, surgery was performed more than 10 weeks following completion of radiotherapy. In both instances, this was due to initial refusal of the patient to have surgery.

The sites of primary tumors and extent of neck disease are shown in Table 2. Four of the patients had occult primary tumors. The most common site was the tonsil (8), followed by the base of the tongue (6), supraglottis (4), nasopharynx (3), and pyriform sinus (1). The Figure shows the sites of neck metastases prior to irradiation. Four patients had multiple sites. Two nodes were located in the submandibular triangle, 5 were upper jugular, 15 were jugulodigastric, and 1 was posterior triangle. None were low jugular, and 7 were not specified. In all cases the histologic diagnosis was squamous cell carcinoma. The grades of differentiation of the carcinomas included 1 carcinoma in situ, 1 well differentiated, 8 moderately differentiated, 4 moderate to poorly differentiated, and 12 poorly differentiated. The doses of radiation received ranged from 6,000 to 7,560 cGy (median 7,000 cGy) in the primary site and from 4,500 to 7,000 cGy (median 6,000 cGy) in the neck. Adjuvant chemotherapy was also used in 2 cases.

TABLE 2. RELATIONSHIP BETWEEN PRIMARY SITE AND N STAGE

	N2a	*N2b*	*N2c*	*N3*	*Nx*
Tonsil	6	0	0	1	1
Base of tongue	2	1	0	1	2
Supraglottis	1	1	1	1	0
Nasopharynx	2	0	0	0	1
Pyriform sinus	1	0	0	0	0
Unknown	2	0	0	2	0

Data are numbers of patients (N = 26).



Sites of neck metastases. Two patients had submandibular triangle metastases; 5, upper jugular; 15, jugulodigastric; none, low jugular; 1, posterior triangle; and 7, unknown. Four had multiple sites.

RESULTS

Following radiotherapy, 11 of the 26 patients were judged to have had a complete clinical response, with no palpable neck disease. In most cases, this was further confirmed with radiologic imaging studies. On repeat endoscopy following radiotherapy, 25 of the 26 patients had negative biopsies of their primary site (or were judged to have negative findings on laryngoscopy, in the cases of the unknown primary tumors). One patient had a positive biopsy of the epiglottis, and a total laryngectomy was attempted but ultimately aborted because he was found intraoperatively to have unresectable neck disease. The remaining 25 patients underwent a neck dissection only. Four patients underwent radical neck dissection, 7 patients underwent modified radical neck dissection (MRND) sparing cranial nerve (CN) XI, 5 patients underwent MRND sparing CN XI and the sternocleidomastoid (SCM) muscle, 8 patients underwent MRND sparing CN XI, the SCM muscle, and the internal jugular (IJ) vein, 1 patient underwent bilateral MRND sparing CN XI on 1 side and CN XI and the IJ vein on the other side, and 1 patient had a partial (suprahyoid) neck dissection that was aborted after tumor was found to be adherent to the base of the skull.

Overall, 13 of the 26 (50%) neck dissections showed viable carcinoma on histopathologic examination. Among the 15 patients who had clinical evidence of residual neck disease, 9 (60%) had histologic evidence of carcinoma. Among the 11 patients who were considered preoperatively to have had a complete response to irradiation, 4 (36%) showed evidence of carcinoma on histologic examination of their neck lymph node specimens. There was no apparent relationship between N stage and pathologic response in the neck.

The morbidity of preoperative radiotherapy followed by surgery appeared to be acceptable. Most patients suffered some degree of xerostomia, dysphagia, and mucositis from the radiation. One patient required gastrostomy tube placement for severe dysphagia. Operating in an irradiated field did not lead to complications in this small series. There were no fistulas or wound breakdowns. Several patients complained of shoulder and arm immobility that usually resolved.

Follow-up of these patients was obtained from data from the UCLA tumor registry and medical records. The range of follow-up was from 3 months to 10 years with a mean of 2 years 8 months. Seventeen patients were alive and free of disease at last follow-up. Five patients died but were free of disease at time of death. Three patients died with disease. Of these 3 patients, 2 had unresectable neck disease at the time of initial operation, while 1 died of a recurrence at the primary site. Only 1 patient in our series has had a recurrence in the neck, occurring 18 months following his neck dissection.

DISCUSSION

For small tumors of the oral cavity, surgical excision can be carried out with minimal functional disability. However, for many other small tumors of the head and neck, radiotherapy is usually preferable for preserving organ function. When patients present with enlarged neck nodes arising from small or occult primary carcinomas of the head and neck, the primary tumor can be treated with irradiation, but combined irradiation and surgery is often required for treatment of the neck. For these patients, there are 3 commonly employed treatment strategies: 1) neck dissection followed by radiotherapy to the neck and primary site; 2) radiotherapy to the primary site and neck (if there is residual neck disease, a neck dissection is performed; if there is no residual neck disease, the patients are observed clinically, with surgery reserved for later documented recurrence); and 3) radiotherapy to the primary site and neck followed by planned neck dissection. We present a series of 26 patients who over the past 10 years were treated with the third strategy.

Whether one should perform neck dissection followed by irradiation or irradiation followed by surgery remains an ongoing subject of debate.[2] The advantages of performing neck dissection following irradiation are several. First, administering radiotherapy right away avoids any delay in treating the primary site. Second, with advanced cervical metastases, extranodal spread and fixation to the carotid sheath can occur, making an initial neck dissection very difficult. Following radiotherapy, a neck dissection can often be performed without carotid artery sacrifice.[3] Third, radiotherapy before surgery may allow for higher frequency of preservation of the SCM muscle and CN XI during the subsequent neck dissection. Finally, completing definitive radiotherapy prior to surgery allows easy assessment of the treatment result to the primary tumor, since an endoscopy with frozen section biopsies of the primary site is performed at the time of the planned neck dissection. This method obviously requires a high level of reliability of frozen section diagnoses, which can be difficult to make, especially in an irradiated field. Frozen section diagnosis may vary in reliability from center to center, but it should agree with the final pathologic diagnosis in more than 97% of cases.[4] In our series, there were no discrepancies between the frozen section and final pathologic diagnoses.

Those who advocate performing a neck dissection first have argued that doing so avoids the increased surgical morbidity associated with operating in an irradiated field. While surgery following radiotherapy is certainly more difficult, in our series no serious surgical complications occurred; this finding suggests that the morbidity of operating in an irradiated field is acceptable. The timing of surgery is important, with the best results occurring when neck dissection is performed approximately 6 to 8 weeks following completion of radiotherapy, before development of the mature radiation-induced fibrosis that would be encountered if surgery was performed later. On the other hand, surgery performed earlier would likely be accompanied by diffuse hyperemia and increased blood loss. Another proposed advantage of performing a neck dissection first is that when the involved nodes are completely resected and without capsular involvement, the amount of radiotherapy needed to treat the neck could be reduced.[5] The benefit of this reduction, however, is likely marginal, since the primary site still requires full-dose radiotherapy and most of the morbidity of radiotherapy is associated with treatment of the primary tumor. Finally, there is a risk that a complete response to radiotherapy may lull the patient and the radiation oncologist into a false sense of security that the neck disease is cured, and cause a neck dissection not to be performed. This can almost always be avoided when there is consensus between the surgeon and radiation oncologist prior to the initiation of treatment.

In a recent trial of stage 3 and 4 head and neck cancer patients who received radiotherapy or combined chemotherapy and radiotherapy, a planned neck dissection was found to reduce the incidence of neck recurrence regardless of clinical response to the radiotherapy.[6] As in our series, among those patients who had a complete clinical response to irradiation and who underwent subsequent neck dissection, a significant proportion had positive nodes on pathologic examination. Also of note, of the patients who did not undergo planned neck dissection and developed neck recurrence, none could be successfully salvaged.

It has been our policy to perform a neck dissection 6 to 8 weeks following completion of radiotherapy, regardless of whether there is clinically detectable residual neck disease. Of the patients in our series who were treated according to this protocol, only 1 suffered a recurrence in the neck. While some would consider close observation for patients who have had a complete clinical response to radiotherapy,[7] we believe that there is a significant enough incidence of microscopic metastatic disease to warrant performing a planned neck dissection. In our series, 11 patients had no clinical or radiologic evidence of neck disease following radiotherapy. A neck dissection was performed on each of these patients. Upon histopathologic examination of their neck nodes, nearly 40% had evidence of metastatic cancer. It is generally regarded that a greater than 25% risk of microscopic metastatic disease is an adequate indication to perform a neck dissection.[8,9] Performing a planned neck dissection in these patients diminishes the potential problem of detection of late recurrence following radiotherapy, which can be difficult secondary to radiation-induced fibrosis. Surgical salvage for late recurrences in the neck is very difficult, and these patients are often unresectable. By administering radiotherapy prior to surgery, one may increase the likelihood that modifications can be made in the standard radical neck dissection to allow the preservation of the spinal accessory nerve and/or SCM muscle, thus reducing the morbidity of the operation.

When patients have fixed nodes or carotid sheath involvement, the prognosis is poor, and it is unclear whether neck dissection, even when made feasible by prior radiotherapy, can improve patient survival. However, we believe the benefit of removing cancer from the neck outweighs the minimal morbidity of a neck dissection. In addition, because it is often difficult to determine whether there is carotid artery involvement preoperatively, the neck should be explored in these patients with advanced cervical metastases.[10,11]

In conclusion, the findings of this small series suggest that patients who present with small or occult primary squamous cell carcinomas of the head and neck with advanced cervical metastases should be treated with initial radiotherapy to the primary site and neck, followed by planned neck dissection even in the absence of clinically detectable residual neck disease.

REFERENCES

1. Yuen APW, Wei WI, Wong SHW. Critical appraisal of watchful waiting policy in the management of N0 neck of advanced laryngeal carcinoma. Arch Otolaryngol Head Neck Surg 1996;122:742-5.

2. Byers RM, Clayman GL, Guillamondegui OM, Peters LJ, Goepfert H. Resection of advanced cervical metastasis prior to definitive radiotherapy for primary squamous carcinomas of the upper aerodigestive tract. Head Neck 1992;14:133-8.

3. Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. Head Neck 1989;11:400-4.

4. Gandour-Edwards RF, Donald PJ, Wiese DA. Accuracy of intraoperative frozen section diagnosis in head and neck surgery: experience at a university medical center. Head Neck 1993;15:33-8.

5. Verschuur HP, Keus RB, Hilgers FJM, Balm AJM, Gregor RT. Preservation of function by radiotherapy of small primary carcinomas preceded by neck dissection for extensive nodal metastases of the head and neck. Head Neck 1996;18:277-82.

6. Lavertu P, Adelstein DJ, Saxton JP, et al. Management of the neck in a randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer. Head Neck 1997;19:559-66.

7. Peters LJ, Weber RS, Morrison WH, Byers RM, Garden AS, Goepfert H. Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. Head Neck 1996;18:552-9.

8. Shah JP, Lydiatt W. Treatment of cancer of the head and neck. CA Cancer J Clin 1995;15:352-68.

9. Snow GB, Patel P, Leemans CR, Tiwari R. Management of cervical lymph nodes in patients with head and neck cancer. Eur Arch Otorhinolaryngol 1992;249:187-94.

10. Ward PW. Oncologic issues relating to neck dissection. In: Pillsbury HC, Goldsmith MM, eds. Operative challenges in otolaryngology–head and neck surgery. Chicago, Ill: Year Book Medical Publishers, 1990:407-9.

11. DeSanto LW. Oncologic issues relating to neck dissection. In: Pillsbury HC, Goldsmith MM, eds. Operative challenges in otolaryngology–head and neck surgery. Chicago, Ill: Year Book Medical Publishers, 1990:410-21.

Ann Otol Rhinol Laryngol 108:1999

CLINICAL APPLICATIONS OF TRANSIENTLY EVOKED OTOACOUSTIC EMISSIONS IN THE PEDIATRIC POPULATION

SUKGI S. CHOI, MD
IRENE A. PAFITIS, PHD
GILBERT R. HERER, PHD
GEORGE H. ZALZAL, MD
KANTILAL M. PATEL, PHD
WASHINGTON, DC

Our objectives were 1) to determine whether transiently evoked otoacoustic emissions (TEOAEs) are affected by the status of the tympanic membrane (TM) and middle ear (ME) as determined by clinical examinations and tympanograms; 2) to determine the efficacy of TEOAEs in detecting hearing loss; and 3) to determine the relative effects of the ME status and hearing loss on TEOAEs. In a prospective observational study in a tertiary care children's hospital, 89 patients (169 ears; 9 ears eliminated from analyses) were examined by 2 attending pediatric otolaryngologists for otologic conditions and underwent audiologic evaluations including TEOAEs from August 1994 through May 1995. The main outcome measures were presence or absence of TEOAE whole reproducibility (WR) and reproducibility (R) at 2 kHz. Statistical analyses showed that of the 8 ME and TM conditions evaluated (normal, TM perforation, pressure equalization [PE] tube, TM retraction, tympanosclerosis, TM atrophy, ME effusion, surgery other than PE tube insertion), only the presence of ME effusion and normal examination findings had a significant effect on the results of WR and R at 2 kHz. Of the 6 different types of tympanograms evaluated (A, B, C, AD, AS, B with large volume), type A, B, and C tympanograms had a significant effect on WR and types A and B had a significant effect on R at 2 kHz. Hearing losses ≥25 dB hearing level (HL) at any of the 5 frequencies (0.25, 0.5, 1, 2, and 4 kHz) were well predicted by the absence of WR and R at 2 kHz. When clinical examination and impedance data were evaluated simultaneously with hearing status, hearing status had a greater effect on WR and R at 2 kHz. We conclude that type B and C tympanograms and the presence of ME effusion (which reflect abnormal ME status) have an adverse effect on TEOAEs. However, the presence of hearing loss is the most significant predictor of TEOAE results. The TEOAE WR and R at 2 kHz are effective in identifying patients with normal hearing and with hearing losses ≥25 dB HL.

KEY WORDS — hearing loss, middle ear, transiently evoked otoacoustic emissions, tympanic membrane.

INTRODUCTION

Otoacoustic emissions (OAEs) were first described by Kemp[1] in 1978. These low-level sounds are produced by the micromechanical activities of the outer hair cells and can be measured with a microphone placed in the external auditory canal. They have gained wide acceptance for use in infant hearing screening for the following reasons: noninvasiveness; accuracy; objectivity; short testing time; and minimal training needed for the test givers.[2]

There are several types of OAEs, including spontaneous (SOAEs), stimulus frequency, transiently evoked (TEOAEs), and distortion product (DPOAEs) OAEs. Spontaneous otoacoustic emissions are present in approximately 40% to 75% of normal hearing ears and occur without any external stimulation.[1,3] Current clinical research is focusing on TEOAEs and DPOAEs. The TEOAEs are elicited by a click stimulus and are present in nearly all healthy ears. Hearing loss of >30 dB hearing level (HL) has been found to obliterate these emissions.[4] The TEOAEs have clinical use in hearing screening, in differentiating cochlear from neural hearing loss, and in monitoring cochlear function.

Several studies indicate that TEOAEs are able to detect hearing loss of ≥30 dB HL,[1,5-7] whereas others found that hearing loss >20 dB HL[8,9] can be detected by TEOAEs. In addition, the literature on the effect of different middle ear (ME) conditions on TEOAEs is sparse, unclear, and at times contradictory.[5,8,10-12] Therefore, the effects of tympanic membrane (TM) retraction, ME fluid, pressure-equalizing (PE) tubes, and TM perforation on TEOAEs are not clear. This study was undertaken to determine the association of ME status (assessed clinically and by acoustic immittance) with the outcome of TEOAE recordings, to determine the level of hearing loss that can be identified by TEOAEs, and to determine whether ME dysfunction or hearing loss has a greater impact on the presence of TEOAEs.

MATERIALS AND METHODS

Data collection was undertaken with an approved Institutional Review Board protocol on 89 children

---

From the Department of Pediatric Otolaryngology–Head and Neck Surgery (Choi, Zalzal), the Department of Hearing and Speech (Pafitis, Herer), and Children's Research Institute, Research Center for Health Services and Clinical Research (Patel), Children's National Medical Center, George Washington University, Washington DC.

Presented at the meeting of the American Society of Pediatric Otolaryngology, Orlando, Florida, May 6-9, 1996.

CORRESPONDENCE — Sukgi S. Choi, MD, Dept of Otolaryngology–Head and Neck Surgery, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010.

(178 ears) seen at the Departments of Otolaryngology and Hearing and Speech at the Children's National Medical Center between August 1994 and May 1995. Nine ears from the 89 subjects were eliminated from all analysis because complete ILO88 data (ie, 260 quiet samples) could not be measured in the external auditory canal; thus, the final sample size was 169. Subjects ranged in age from 8 months to 18.1 years, with a mean age of 5.6 years.

All subjects received comprehensive otologic evaluation including medical history and pneumatic otoscopy by 1 of the 2 attending pediatric otolaryngologists participating in this study. Results of pneumatic otoscopy and history were used to classify the ears into normal, ME effusion, TM retraction (>50%), tympanosclerosis (>30%), TM atrophy, TM perforation, PE tube, and previous otologic surgery (other than PE tube) clinical categories.

Subjects then received complete audiologic evaluations conducted by certified audiologists experienced in the assessment of children. Audiologic testing included assessment of hearing sensitivity using techniques appropriate for the age of each subject and TEOAE testing, as well as assessment of ME status using immittance measures. The same audiologist performed all portions of the audiologic evaluation for each subject.

Audiologic evaluations were conducted in a double-walled sound suite. All audiometric equipment was calibrated according to American National Standards Institute 1987 standards. Audiologic evaluations were carried out with either the Grason Stadler GSI 17 clinical audiometer or the Beltone 120 portable audiometer, or a combination of both, depending on the testing method. Immittance testing was conducted with the Grason Stadler GSI 33 Middle Ear Analyzer. The audiologic evaluation method used was dependent upon the age and developmental level of each subject. Most subjects were successfully tested with either standard or conditioned play audiometry. Some of the younger subjects were assessed with visual reinforcement audiometry. When air conduction thresholds were out of the normal hearing range (ie, >20 dB HL), bone conduction thresholds were obtained. When masking was required, a level of 60 dB HL effective masking was utilized. This procedure was chosen in order to facilitate testing in this young population. This level of masking was not felt to result in overmasking in any subjects. Immittance testing including tympanometry and acoustic reflex testing was conducted for all children participating in the study. However, acoustic reflex testing could not be completed in many subjects, and therefore, this information was not used in data analysis.

The TEOAE testing was conducted in another sound-treated room within the Hearing and Speech Department. The TEOAEs were recorded with the Otodynamics ILO88 Otoacoustic Emission Test System and the Quickscreen Program (version V4.20B).[13] The stimulus presentation, data recording, averaging, noise suppression, and spectral analysis were carried out at default settings. Either an infant or a child probe was utilized depending upon the age of the subject. A probe cavity calibration test was routinely performed at the beginning of each testing day. The Quickscreen program delivers a 0.1-millisecond broadband click at a rate of 80 clicks per second. The peak stimulus intensity was automatically adjusted to approximately 80 dB sound pressure level (SPL).[6] The noise rejection level was set such that any recordings with a noise level of >50 dB SPL were not included in calculating the average response. The Quickscreen program was utilized in this investigation because it reduces the amount of low-frequency noise, such as movement artifact, and therefore speeds up the data collection process. The TEOAE recordings were considered to be technically satisfactory if the peak stimulus intensity was between 78 and 83 dB SPL, the noise rejection was <50 dB SPL, and 260 responses were obtained.

The subjects' ears were divided into ears with normal hearing, with conductive hearing loss, with sensorineural hearing loss, and with mixed hearing loss. Subjects were considered to have a hearing loss if any threshold between 250 and 4,000 Hz was >20 dB HL. The nature of each subject's hearing loss was determined by examination of the audiogram and the presence or absence of an air-bone gap. Earphone testing could not be completed in 38 ears. Although sound field thresholds were obtained for these subjects, these results were not used in the analysis of hearing threshold data.

Immittance results were divided into 6 categories. Tympanograms were classified as type A if a clear peak of maximum compliance was present between –199 and +50 decapascals (da Pa) with volumes of 0.2 to 1.8 mL; type B if there was no clear peak of maximum compliance; type C if a clear peak of maximum compliance was located at a negative pressure of –200 da Pa or greater; type AD if the peak of maximum compliance exceeded 1.8 mL and was located at a pressure between –200 and +50 da Pa; type AS if the peak of maximum compliance was <0.2 mL and was located between –200 and +50 da Pa; and type B (flat with large volume) if there was no clear peak of maximum compliance and the volume was >2.0 mL due to the presence of a patent PE

TABLE 1. PNEUMATIC OTOSCOPY FINDINGS

	Ears		
Clinical Status	*No.*	*%*	*95% CI*
ME effusion	73	40.3	35.7 - 51.0
Normal	37	20.4	16.1 - 29.0
PE tube	34	18.8	14.5 - 27.1
TM retraction	13	7.2	4.3 - 13.1
Tympanosclerosis	8	4.4	2.2 - 9.4
Surgery other than PE tubes	7	3.9	2.1 - 8.3
TM perforation	6	3.3	1.7 - 7.6
TM atrophy	3	1.7	0.6 - 5.1
Total ears	181		

CI — confidence interval, ME — middle ear, PE — pressure equalization, TM — tympanic membrane.

tube or perforation.

In analyzing the TEOAE results, whole reproducibility (WR) and reproducibility (R) at 2 kHz were used as indicators of present emissions. A WR $\geq 60\%$ and an R at 2 kHz $\geq 50\%$ were considered to indicate the presence of emissions and therefore no hearing loss. The rationale for choosing these criteria is given in the Discussion.

Pearson's correlation analysis determines the presence of a linear relationship between 2 variables. This analysis was used to determine whether there was an agreement between the results of clinical examinations and tympanograms, and the presence of significant correlation was tested by the *t*-test.[14] Fisher's exact test was chosen to analyze the association between the outcome measures (WR and R at 2 kHz) and the clinical status of the ears, the tympanograms, and the status of hearing loss. This test was chosen because it is a powerful, nonparametric test that can be utilized with a small sample size.[14] Linear regression analysis was used to determine the association between the outcome measures and the status of hearing loss and clinical status, and between the outcome measures with the tympanogram types and the status of hearing loss. Regression analysis eliminates the effect of the variables on each other so that the relative contribution of each variable on the outcome measures can be determined.[15] The statistical significance of the associations found in the linear regression analysis was then tested by Wald's χ^2 test.[15] The level of significance was chosen at .05.

TABLE 2. SUMMARY OF TYMPANOGRAMS

	Ears		
Tympanogram Type	*No.*	*%*	*95% CI*
A	60	35.5	28.4 - 43.3
B	50	29.6	23.0 - 37.2
C	16	9.5	5.7 - 15.2
AD	4	2.4	1.0 - 5.9
As	1	0.6	0.1 - 3.3
B with large volume	38	22.5	16.6 - 29.7
Total	169		

TABLE 3. PEARSON'S CORRELATION OF CLINICAL EXAMINATION AND TYMPANOGRAMS

Clinical Exam and Tympanogram	*Pearson's Correlation*	
	Correlation %	*p**
Normal and type A	65	.0001
Fluid and type B	66	.0001
Tube or perforation and type B with large volume	90	.0001
Retraction and type C	13	.0820
Tympanosclerosis and type As	−2	.8244
Atrophy and type AD	27	.0003

*$p < .05$ is statistically significant.

RESULTS

The summary of clinical findings in the 169 ears is shown in Table 1. The total number of diagnoses equals 181 ears. The numbers and types of tympanograms seen in this population are summarized in Table 2. Of the 169 ears, 38 ears had only sound field results. In the remaining 131 ears, 88 (67.2%) had normal hearing, 38 (29.0%) had conductive hearing loss, 4 (3.1%) had sensorineural hearing loss, and 1 (0.7%) had mixed loss.

To test the correlation between the results of the clinical examination and immittance, Pearson's correlation analysis[14] was done (Table 3). A significant positive correlation was seen in cases of normal ME, ME effusion, TM atrophy, and PE tube or TM perforation with tympanogram types A, B, AD, and B with large volume, respectively. Correlations for TM retraction and tympanosclerosis with tympanogram types C and As were low, and no significance was found on the *t*-test.

All 169 ears were used in the first 2 analyses (Tables 4 and 5). The results shown in Table 4 — predicting WR and R at 2 kHz by using clinical status of

TABLE 4. ASSOCIATION OF CLINICAL EXAMINATION WITH WR AND R AT 2 KILOHERTZ

	p on Fisher's Exact Test*	
Ear Status	*WR*	*R at 2 kHz*
Normal	<.001	<.001
ME effusion	<.001	<.001
TM perforation	.410	.682
PE tube	.116	.444
TM retraction	.560	.398
Tympanosclerosis	1.000	1.000
TM atrophy	1.000	.616
Previous ear surgery	.856	1.000

WR — transiently evoked otoacoustic emissions (TEOAEs) whole reproducibility, R — reproducibility.

*$p < .05$ is statistically significant.

TABLE 5. ASSOCIATION OF TYMPANOGRAMS WITH WR AND R AT 2 KILOHERTZ

	p on Fisher's Exact Test*	
Tympanograms	*WR*	*R at 2 kHz*
A	<.001	<.001
B	<.001	<.001
C	<.006	1.000
AD	.153	1.000
As	.379	.491
B with large volume	.090	.713

*$p < .05$ is statistically significant.

the TM and ME as determined otoscopically — were tested with Fisher's exact test. There was a significant association between a normal ME and the presence of emissions. In addition, there was a significant association between the presence of ME effusion and the absence of emissions. No other significant associations were found.

The association between the 6 types of tympanograms and WR and R at 2 kHz was also tested with Fisher's exact test. A significant positive association of a type A tympanogram and a significant negative association of type B and C tympanograms with WR results were seen. In the case of R at 2 kHz, a positive association was seen with a type A tympanogram, and a negative association with a type B tympanogram. No other significant relationships were found (Table 5).

Only 131 ears were used for the next 4 analyses (Tables 6-9), which pertain to hearing thresholds, because in 38 ears only sound field threshold information was available. The objective was to determine the lowest level of hearing loss (≥25 dB HL versus ≥30 dB HL) that can be detected by WR and R at 2 kHz. Specifically, Fisher's exact test was used to test the relationships between a hearing loss of ≥25 dB HL or ≥30 dB HL at the 5 different frequencies (0.25, 0.50, 1, 2, 4 kHz) and WR and R at 2 kHz. The analyses in Tables 6 and 7 indicate that WR and R at 2 kHz can well predict hearing losses of ≥30 dB HL and ≥25 dB HL (at any of the 5 frequencies tested). Stated differently, these results indicate that the smallest degree of hearing loss that can be detected reliably by WR and R at 2 kHz is a hearing loss of ≥25 dB HL.

TABLE 6. PREDICTION OF HEARING LOSS OF AT LEAST 25 DECIBELS HEARING LEVEL BY WR AND R AT 2 KILOHERTZ

	p on Fisher's Exact Test*	
Frequency	*WR*	*R at 2 kHz*
250 Hz	<.001	<.001
500 Hz	<.001	<.001
1 kHz	<.001	<.001
2 kHz	<.001	<.001
4 kHz	<.001	<.001

*$p < .05$ is statistically significant.

TABLE 7. PREDICTION OF HEARING LOSS OF AT LEAST 30 DECIBELS HEARING LEVEL BY WR AND R AT 2 KILOHERTZ

	p on Fisher's Exact Test*	
Frequency	*WR*	*R at 2 kHz*
250 Hz	.003	<.001
500 Hz	<.001	<.001
1 kHz	<.001	<.001
2 kHz	<.001	<.001
4 kHz	<.001	<.001

*$p < .05$ is statistically significant.

TABLE 8. RELATIVE EFFECT OF CLINICAL EXAMINATION AND HEARING LOSS OF AT LEAST 25 DECIBELS HEARING LEVEL ON WR AND R AT 2 KILOHERTZ FOR EACH CLINICAL STATUS

	p for WR*		*p* for R at 2 kHz*	
	Clinical Status	*≥25 dB HL*	*Clinical Status*	*≥25 dB HL*
Normal	.0041	.0001†	.0017	.0001†
Fluid	.0622	.0001	.0139	.0001†
Tympanosclerosis	.3015	.0001	.2721	.0001
Retraction	.6794	.0001	.8651	.0001
Atrophy	.4518	.0001	.9643	.0001
Tube	.5783	.0001	.7457	.0001
Perforation	.4123	.0001	.6781	.0001
Surgery	.5314	.0001	.3474	.0001

*Logistic linear regression analysis by Wald's χ^2; $p < .05$ is statistically significant.

†Denotes parameter that has greater effect on presence of WR or R at 2 kHz when both clinical status and hearing loss have significant association with WR or R at 2 kHz outcome.

To determine whether the clinical status of the ME and the TM or the presence of hearing loss played a greater role in determining WR and R at 2 kHz, 2 analyses were completed. First, the simultaneous effect of the ME status as determined by clinical examination and hearing status on WR and R at 2 kHz was analyzed by logistic linear regression (Table 8). The status of hearing loss always showed a negative association with WR and R at 2 kHz. The only clinical status that showed any significant association with the WR outcome was the normal category — and with R at 2 kHz, the normal and ME fluid categories. In all of the 3 cases (with a footnote on Table 8) in which both the status of hearing loss and the clinical status had a significant association with the outcome measures (WR and R at 2 kHz), hearing loss always had a greater effect on the outcome measures as determined by the regression coefficient. Similarly, the simultaneous effect of the ME status

TABLE 9. RELATIVE EFFECT OF TYMPANOGRAM AND HEARING LOSS OF AT LEAST 25 DECIBELS HEARING LEVEL ON WR AND R AT 2 KILOHERTZ FOR EACH TYMPANOGRAM TYPE

	p for WR*		*p* for R at 2 kHz*	
	Tympanogram	*≥25 dB HL*	*Tympanogram*	*≥25 dB HL*
A	.0435	.0001†	.0001	<.0001†
B	.0387	.0001†	<.0001§	.0001
C	.0146	.0001†	.7657	.0001
AD	.4355	.0001	.4463	.0001
B with large volume	.5068	.0001	.4219	.0001

*Logistic linear regression analysis by Wald's χ^2; $p < .05$ is statistically significant.

†Denotes parameter that has greater effect on presence of WR or R at 2 kHz when both type of tympanogram and hearing loss have significant association with WR or R at 2 kHz outcome.

§Denotes that type of tympanogram had greater effect than hearing loss on outcome measures.

as determined by 6 types of tympanograms and the hearing status on WR and R at 2 kHz was analyzed (Table 9). Type AS tympanograms were too few in number (1) for valid analysis. The status of hearing loss was always negatively associated with the outcome measures. Type A, B, and C tympanograms had a significant effect on WR, and types A and B had a significant effect on R at 2 kHz. In 4 of 5 cases (with a footnote on Table 9) in which both the status of hearing loss and the type of tympanogram had a significant association with the outcome measures (WR and R at 2 kHz), the status of hearing loss had a greater effect on the outcome of WR and R at 2 kHz. In the case of type B tympanogram and hearing loss (with a footnote on Table 9), the tympanogram had a greater effect on R at 2 kHz than did the status of hearing loss.

DISCUSSION

For the previously mentioned reasons, TEOAEs are widely used for hearing screening. The limitations of TEOAEs are that they cannot provide information on the degree of hearing loss, they cannot be used to reconstruct a pure tone audiogram, and they do not distinguish conductive from sensorineural hearing loss.[4,16-19] In addition, there are several areas of controversy in the use of TEOAEs, concerned with the smallest level of hearing loss detectable by TEOAEs, the effect of various ME conditions on TEOAEs, and the relative effects of ME dysfunction and hearing loss on TEOAEs.

Several different parameters of TEOAEs have been proposed as a means of determining the presence or absence of emissions.[4,8-11,18] The reproducibility of the TEOAE response is frequently used as a means of making this determination. The WR is calculated by comparing in the temporal domain the 2 averaged emission waveforms, each of which is based on a complete run of an n = 260 stimulus set. The correlation value obtained by point-by-point comparison of the data in the 2 waveforms is the WR expressed in percent.[8,11] Although there are exceptions, generally, a WR that is ≥50% is considered to indicate hearing levels of 30 dB or better.[4,20] Some investigators feel that WR can be used to identify a hearing loss of >20 dB HL or a pure tone average of >40 dB HL in children.[9]

Frequency-specific reproducibility is automatically calculated by the ILO88 software. A study has shown that an R at 2 kHz of 50% or higher is the most efficient of all TEOAE measurements in separating normal ears from ears with a >20 dB HL hearing loss regardless of the frequency or frequencies at which the hearing loss occurred.[8]

A WR of ≥60% and an R at 2 kHz of ≥50% were chosen as criteria for assessing the presence or absence of emissions. These criteria were chosen because they had been previously demonstrated to indicate a hearing loss of ≥30 dB.[4,8,9,20] Analyses of this study show that WR and R at 2 kHz were equally effective in identifying hearing losses of ≥25 dB HL and ≥30 dB HL. Therefore, the lowest level of hearing loss detectable by TEOAEs in the present study appears to be ≥25 dB HL. This finding is in agreement with those of Prieve et al[9] and Glattke et al.[8]

The TEOAEs are transmitted from the cochlea through the ossicles and TM and measured in the external auditory canal. Thus, any ME disorder or obstruction of the external auditory canal can potentially impede TEOAE transmission. Therefore, it is recommended that TEOAE testing be completed in conjunction with immittance testing.[10,21,22] Several studies have shown that artificial manipulation of the ME compliance, in both the negative and positive directions, causes a decrease in OAE response levels.[23-25] Owens et al[10] found that ears with type B and C tympanograms had absent or reduced OAE amplitudes and that ears with PE tubes had lower levels than normal ears, but had higher levels than ears with untreated ME disease. Glattke et al[8] reported that a type B tympanogram precluded the recording of TEOAEs. However, Amedee[12] discovered that it was not the presence of ME effusion or a type B tympanogram, but the quality of the ME fluid, that affects the TEOAE outcome. Owens et al[5] concluded that in general, the use of TEOAEs is contraindicated in the presence of any ME disease. On the other hand, Hall et al[11] proposed that OAE testing should not be avoided in the presence of ME disease.

In the present study, pneumatic otoscopy and immittance testing were completed on all patients as measures of ME function. Any debris in the external auditory canal was removed and should not have affected the test outcome. Significant correlations between the clinical examination and the type of tympanogram were seen in cases of normal ears, ears with ME effusion, and ears with PE tubes or perforations.

When the relationships between the clinical status of the ear as determined by pneumatic otoscopy and WR and R at 2 kHz were examined, normal ears were associated with the presence of WR and R at 2 kHz and ME effusion was associated with the absence of WR and R at 2 kHz. Neither TM retraction nor the presence of PE tubes or perforations were found to have a significant association with TEOAE results. Whether this lack of significant association of TM retraction with the outcome of TEOAE testing was due to an inaccuracy of the clinical observation or the fact that TM retraction was often (7/13) seen in conjunction with other ear conditions is unknown. The present findings confirm that although TEOAE testing may be used in ears with PE tubes, perforations, and TM retractions, it may not be a useful procedure in ears with ME effusion.

When the relationship between the type of tympanogram and WR and R at 2 kHz was examined, type A tympanograms were found to be associated with present emissions and type B tympanograms with absent emissions. Additionally, a significant negative association was found between a type C tympanogram and WR. No other significant association was present. These findings confirm that TEOAEs can be used to screen for hearing loss in normal ears and ears with PE tubes or perforations, but may not be useful in ears with ME effusion. Because significant associations were seen more often with immittance results than with the results of clinical examination, tympanograms may be a more accurate means of predicting ME dysfunction. Similar findings have been previously reported.[26]

Contrary to the work of Owens et al,[5] both Lonsbury-Martin et al[21] and Pröschel and Eysholdt[22] found that the effect of ME function on TEOAEs is not simply related to the immittance results. The latter 2 investigators believe that the degree of hearing loss caused by ME dysfunction may influence the results of TEOAE testing. The findings of the present study agree with this observation in that the presence of hearing loss had a greater impact on the outcome of WR and R at 2 kHz than did ME status as assessed by either otoscopy or tympanograms.

CONCLUSION

Assessment of TEOAEs is a valuable hearing screening tool, although it does have certain limitations: TEOAEs do not provide information on the degree or configuration of hearing loss, nor do the results distinguish sensorineural from conductive hearing loss. Therefore, an abnormal TEOAE result must be followed by additional testing.

The results of this investigation indicate that a hearing loss of ≥25 dB HL at any of the 5 frequencies (0.25, 0.5, 1, 2, 4 kHz) is well predicted by the absence of WR and R at 2 kHz. Assessment of TEOAEs can be used in normal-appearing ears (no ME disease), but its utility may be limited in ears with PE tubes or perforations, as well as ears with a retracted TM or tympanosclerosis. The presence of ME effusion or a type B tympanogram will impede measurement of these emissions. Although the transmission of TEOAEs may be hampered by ME dysfunction, it is the hearing loss caused by the ME dysfunction that has a greater impact on the TEOAEs.

REFERENCES

1. Kemp DT. Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am 1978;64:1386-91.

2. Lonsbury-Martin BL. Introduction to otoacoustic emissions. Am J Otol 1994;15(suppl 1):1-3.

3. Penner MJ, Glotzbach L, Huang T. Spontaneous otoacoustic emissions: measurement and data. Hear Res 1993;68:229-37.

4. Hurley RM, Musiek FE. Effectiveness of transient-evoked otoacoustic emissions (TEOAEs) in predicting hearing level. J Am Acad Audiol 1994;5:195-203.

5. Owens JJ, McCoy MJ, Lonsbury-Martin BL, Martin GK. Influence of otitis media on evoked otoacoustic emissions in children. Semin Hear 1992;13:53-66.

6. Probst R, Harris F. Transiently evoked and distortion-product otoacoustic emissions. Comparison of results from normally hearing and hearing-impaired human ears. Arch Otolaryngol Head Neck Surg 1993;119:858-60.

7. Richardson MP, Williamson TJ, Lenton SW, Tarlow MJ, Rudd PT. Otoacoustic emissions as a screening test for hearing impairment in children. Arch Dis Child 1995;72:294-7.

8. Glattke TJ, Pafitis IA, Cummiskey C, Herer GR. Identification of hearing loss in children and young adults using measures of transient otoacoustic emission reproducibility. Am J Audiol 1995;4:71-86.

9. Prieve BA, Gorga MP, Schmidt A, et al. Analysis of transient-evoked otoacoustic emissions in normal-hearing and hearing-impaired ears. J Acoust Soc Am 1993;93:3308-19.

10. Owens JJ, McCoy MJ, Lonsbury-Martin BL, Martin GK. Otoacoustic emissions in children with normal ears, middle ear dysfunction, and ventilating tubes. Am J Otol 1993;14:34-40.

11. Hall JW, Baer JE, Chase PA, Schwaber MK. Clinical

application of otoacoustic emissions: what do we know about factors influencing measurement and analysis? Otolaryngol Head Neck Surg 1994;110:22-38.

12. Amedee RG. The effects of chronic otitis media with effusion on the measurement of transiently evoked otoacoustic emissions. Laryngoscope 1995;105:589-95.

13. Vohr BR, White KR, Maxon AB, Johnson MJ. Factors affecting the interpretation of transient evoked otoacoustic emission results in neonatal hearing screening. Semin Hear 1993;14:57-72.

14. Armitage P. Statistical methods in medical research. New York, NY: John Wiley & Sons, 1971:135-8, 156-66.

15. Hosmer DW, Lemeshow S. Interpretation of the coefficients of the logistic regression model. In: Barnett V, Bradley RA, Hunter JS, eds. Applied logistic regression. New York, NY: John Wiley & Sons, 1989:38-81.

16. Martin GK, Whitehead ML, Lonsbury-Martin BL. Potential of evoked otoacoustic emissions for infant hearing screening. Semin Hear 1990;11:186-203.

17. Spektor Z, Leonard G, Kim DO, Jung MD, Smurzynski J. Otoacoustic emissions in normal and hearing-impaired children and normal adults. Laryngoscope 1991;101:965-76.

18. Harris FP, Probst R. Reporting click-evoked and distortion-product otoacoustic emission results with respect to the pure-tone audiogram. Ear Hear 1991;12:399-405.

19. Collet L, Veuillet E, Chanal JM, Morgon A. Evoked otoacoustic emissions: correlates between spectrum analysis and audiogram. Audiology 1991;30:164-72.

20. Kemp DT, Bray P, Alexander L, Brown AM. Acoustic emission cochleography. Practical aspects. Scand Audiol Suppl 1986;15(suppl 25):71-96.

21. Lonsbury-Martin BL, Martin GK, McCoy MJ, Whitehead ML. Otoacoustic emissions testing in young children: middle-ear influences. Am J Otol 1994;15(suppl 1):13-20.

22. Pröschel U, Eysholdt U. Evoked otoacoustic emissions in children in relation to middle ear impedance. Folia Phoniatr (Basel) 1993;45:288-94.

23. Naeve SL, Margolis RH, Levine SC, Fournier EM. Effect of ear-canal air pressure on evoked otoacoustic emissions. J Acoust Soc Am 1992;91:2091-5.

24. Trine MB, Hirsch JE, Margolis RH. The effect of middle ear pressure on transient evoked otoacoustic emissions. Ear Hear 1993;14:401-7.

25. Plinkert PK, Bootz F, VoBieck T. Influence of static middle ear pressure on transiently evoked otoacoustic emissions and distortion products. Eur Arch Otorhinolaryngol 1994;*251*: 95-9.

26. Finitzo T, Friel-Patti S, Chinn K, Brown O. Tympanometry and otoscopy prior to myringotomy: issues in diagnosis of otitis media. Int J Pediatr Otorhinolaryngol 1992;24:101-10.

Ann Otol Rhinol Laryngol 108:1999

SMOKING INCREASES FACIAL SKIN FLAP COMPLICATIONS

JOHN B. KINSELLA, FRCS(EDIN)
BELFAST, NORTHERN IRELAND

CHRISTOPHER H. RASSEKH, MD
GALVESTON, TEXAS

ZACHARY D. WASSMUTH, MD
SILVER SPRING, MARYLAND

JAMES A. HOKANSON, PHD
GALVESTON, TEXAS

KAREN H. CALHOUN, MD
GALVESTON, TEXAS

This study was undertaken to determine whether smokers have a higher risk of complications after reconstruction of facial skin defects. Ninety-one patients with facial skin defects reconstructed with local flaps were reviewed retrospectively. Thirty-eight (42%) were active smokers, 12 (13%) had not smoked for at least 1 year prior to surgery, and the rest were nonsmokers. Complications occurred in 23 patients (25%; 37% in smokers, 17% in ex-smokers, and 17% in nonsmokers; $p < .03$). All full-thickness skin losses and all cellulitis occurred in active smokers. We conclude that active smokers are at a higher risk for complications in facial skin flap surgery. That ex-smokers had a complication rate similar to that of nonsmokers suggests that part of smoking's adverse effect on skin flaps may be an acute phenomenon, and that smoking cessation for shorter (<1 year) periods of time before surgery may have a beneficial effect.

KEY WORDS — facial skin flaps, smoking.

INTRODUCTION

Clinicians have long suspected that smoking has an adverse effect on wound healing. Cigarette smoke contains more than 4,000 toxic constituents, and of these, nicotine and carbon monoxide are thought to be especially detrimental to tissue oxygenation and wound healing.[1] Although Mosley and Finseth[2] noted an association between cigarette smoking and poor wound healing as long ago as 1977, this relationship has not been extensively studied to date.[3]

Smoking has been shown to have an adverse effect on skin flap survival in experimental animals.[4-6] Clinical studies have demonstrated a higher rate of flap necrosis among smokers undergoing rhytidectomy.[7,8] Goldminz and Bennett[9] have reported that smokers are at increased risk of developing necrosis of full-thickness skin grafts and local flaps. The current study was undertaken to determine if smokers have a higher risk of complications after local skin flap reconstruction of facial defects.

METHODS

A retrospective review was performed on all patients undergoing local skin flap reconstruction of facial skin defects by the Otolaryngology Service at the University of Texas Medical Branch, Galveston, between January 1989 and December 1993. All reconstructions were carried out by staff or residents under the supervision of the senior author (K.H.C.). One hundred eight consecutive patients were identified, and 12 of these were excluded from further analysis because of risk factors for impaired wound healing (diabetes mellitus, collagen vascular disease, previous radiotherapy, and recent use of systemic steroids). A further 5 patients were excluded because they lacked a minimum of 3 months' postoperative follow-up. The charts of the remaining 91 patients were reviewed and data were gathered regarding age; sex; tobacco history; cause, location, and size of facial defect; design and size of flap reconstruction; and complications. We also ranked the cosmetic outcome as excellent, good, moderate, or poor, at a minimum of 3 months' postoperative follow-up.

Patients were divided into the following subgroups on the basis of their smoking history: nonsmokers (patients with no smoking history), ex-smokers (smoking history of at least 10 pack years but had quit smoking for at least 1 year before surgery), and active smokers (smoking at the time of surgery).[10] There were no patients who had quit smoking within the year preceding surgery.

All data were entered on a computer-based data

From the Departments of Otolaryngology (Kinsella, Rassekh, Wassmuth, Calhoun) and Preventive Medicine and Community Health (Hokanson). University of Texas Medical Branch, Galveston, Texas. Dr Kinsella is currently at the Department of Otolaryngology–Head and Neck Surgery, Royal Victoria Hospital, Belfast, Northern Ireland.

Presented at the meeting of the American Academy of Otolaryngology–Head and Neck Surgery, New Orleans, Louisiana, September 17-20, 1995.

CORRESPONDENCE — Karen H. Calhoun, MD, Dept of Otolaryngology, University of Texas Medical Branch, Galveston, TX 77555-0521.

TABLE 1. LOCATION OF PRINCIPAL SURGICAL DEFECT, AVERAGE SURFACE AREA OF RECONSTRUCTIVE FLAP, PERCENTAGE ACTIVELY SMOKING, AND COMPLICATION RATE AT EACH SITE

Site	*No. of Defects*	*Average Surface Area of Flap (cm)*	*% Active Smokers*	*Complication Rate (%)*
Nose	40	6	40	15
Cheek	12	9	58	17
Upper lip	9	10	89	33
Temple	9	14	22	44
Lower lip	6	7	17	17
Forehead	4	10	50	50
Scalp	4	18	0	50
Ear	2	10	50	50
Chin	2	10	0	50
Lower eyelid	2	5	50	50
Upper eyelid	1	5	100	100

management program. We performed χ^2 testing to look for a statistical association between individual characteristics, with a p value of <.05 considered significant.

RESULTS

The age range of the study population was 18 to 91 years with a mean of 61 years. The male-to-female ratio was 1.3 to 1. Eighty-seven patients were white and 4 were Hispanic. Forty-one (45%) were nonsmokers and 12 (13%) were ex-smokers. Thirty-eight (42%) were active smokers, with an average history of 45 pack years. Accurate information on passive smoking was not available for this retrospective study. Active smokers were requested to refrain from smoking for 24 hours postoperatively. All 38 patients, however, were still smoking actively at 3 months' follow-up.

Eighty-six percent of the flaps were performed for reconstruction following Moh's micrographic surgery, and 14% after wide local excision. The histologic diagnosis was basal cell carcinoma in 77%, squamous cell carcinoma in 21%, melanoma in 1%, and dermatofibrosarcoma in 1%. Surgery was undertaken for recurrent disease in 14 of the basal cell carcinomas and in 1 of the squamous cell carcinomas.

The blood supply to the flap was axial in 39 patients and random in 52. The flaps were transpositional in 65 patients, and advancement flaps in 25. In 1 patient, we used an island flap.

Twenty-three complications occurred in 23 patients (25%). The site of the surgical defect, surface area of the reconstructive flap, smoking history, and complication rate at each location are shown in Table 1. The complication rate was 37% in active smokers; this was significantly higher than the rate of 17% for both ex-smokers and nonsmokers (p = .03). There was no significant correlation, however, between the quantity of cigarettes consumed by active smokers (ie, the number of pack years) and the development of complications. The distribution of individual complications in smokers, ex-smokers, and nonsmokers is shown in Table 2.

All cases of full-thickness skin loss and all cases of cellulitis occurred in active smokers. Seven patients developed superficial blistering, with partial loss of the epidermis; none of these patients had loss of dermis, and there was only minimal delay of healing in all cases.

Complications were more likely to occur as the surface area of the skin flap increased in size (p = .02). The blood supply (axial or random) and design of the flap (transpositional, advancement, or island) bore no relationship to the incidence of complications. Sex, race, alcohol consumption, and pathologic diagnosis of lesion had no effect on the occurrence of complications. Antibiotics were used as prophylaxis against chondritis in 26 patients in whom there was exposure of or surgery to cartilage, and were not found to have a statistical correlation with the occurrence of complications. Complication rates were similar for primary and recurrent lesions. The occurrence of perioperative complications was associated with a significant deterioration in the final cosmetic outcome, as judged at a minimum of 3 months' follow-up (p = .001).

DISCUSSION

Previous studies have shown that smoking has an adverse effect on wound healing and skin flap survival.[2,4-9] In our series of local skin flap reconstructions of facial defects, the overall complication rate

TABLE 2. SMOKING HISTORY AND COMPLICATIONS

	Full-Thickness Skin Loss	*Partial-Thickness Skin Loss*	*Cyanosis*	*Cellulitis*	*Hematoma*	*Seroma*
Smokers	4	3	1	4	1	1
Ex-smokers	0	1	0	0	1	0
Nonsmokers	0	3	0	0	3	1

Data are numbers of patients.

of 37% among active smokers was significantly higher than the rate of 17% encountered both in ex-smokers and in nonsmokers. All episodes of full-thickness skin loss and all cases of cellulitis occurred among active smokers. As expected, we also found that complications occurred more commonly as the surface area of the skin flap increased ($p = .02$). The final cosmetic result at a minimum of 3 months' postoperative follow-up was significantly worse among those patients who experienced perioperative complications.

Skin flap survival depends on the presence of a well-oxygenated blood supply, particularly in the first 7 days postoperatively.[9,11] The local tissue oxygen tension influences angiogenesis,[12] collagen deposition,[13] and ability to resist infection.[14,15]

Jensen et al[16] reported a rapid and significant fall in the subcutaneous tissue oxygen tension of 8 volunteers in response to smoking cigarettes for a period of 10 minutes. The degree of hypoxia fell within the range associated with poor wound healing in other studies.[13,14] This decrease in oxygen tension lasted for 30 to 50 minutes, and the authors estimated that a typical 1 pack per day smoker would have significant tissue hypoxia for 15 to 20 h/d.

Cigarette smoke contains more than 4,000 recognized toxic constituents, and at least 2 of these, nicotine and carbon monoxide, are thought to adversely affect tissue oxygenation.[1] Nicotine has several actions that may compromise wound healing. It has a direct vasoconstrictive effect on cutaneous blood vessels and also produces a systemic release of catecholamines from the adrenal medulla. These catecholamines tend to increase the heart rate, blood pressure, and oxygen demand.[1,17] Nicotine causes an increase in platelet adhesiveness that may be complicated by thrombotic occlusion and tissue ischemia.[18] Nicotine can also interfere with collagen deposition by inhibiting the proliferation of fibroblasts.[2]

The affinity of carbon monoxide to bind to hemoglobin is 200 times that of its competitor oxygen. In addition, carboxyhemoglobin causes the oxyhemoglobin dissociation curve to shift to the left, decreasing the efficiency of oxygen release into the tissues. Thus, the net effect of carbon monoxide is cellular hypoxia.[5]

The vasoconstrictive effect of nicotine is short-lived. However, the hypoxic effect of cigarette smoke is more prolonged, because of the high affinity between carbon monoxide and hemoglobin, and lasts for up to 48 hours.[19] These reversible vascular effects of cigarette smoking appear to be more important in the development of flap necrosis than the chronic, irreversible atherosclerotic changes.[8]

Inhaled cigarette smoke is only one of many factors that can impair wound healing. We were not surprised to find that complications were more likely to occur as the surface area of our reconstructive flaps increased. Diabetes mellitus, collagen vascular disease, systemic steroids, and radiotherapy can each have an adverse effect, and were therefore factored out of our study.

We found that patients who had ceased smoking for at least 1 year prior to surgery had a complication rate similar to that of nonsmokers. What remains to be determined is whether smoking cessation for mere weeks or days prior to such surgery would also result in a decreased complication rate. However, until the results of further research are available, it would seem prudent to advise patients to abstain from tobacco for at least 2 days prior to surgery and 7 days postoperatively.

REFERENCES

1. US Department of Health, Education and Welfare. The health consequences of smoking: cardiovascular disease. A report of the Surgeon General. Rockville, Md: US Department of Health and Human Services, Public Health Service Office of Smoking and Health. DHSS Publication No. PHS 84-50204, 1983.

2. Mosley L, Finseth F. Cigarette smoking: impairment of digital blood flow and wound healing in the hand. Hand Clin 1977;98:97-101.

3. Silverstein P. Smoking and wound healing. Am J Med 1992;93(suppl 1A):22S-24S.

4. Lawrence WT, Murphy RC, Robson MC, Heggers JP. The detrimental effect of cigarette smoking on flap survival: an experimental study in the rat. Br J Plast Surg 1984;37:216-9.

5. Nolan J, Jenkins RA, Kurihara K, Schultz RC. The acute effects of cigarette smoke exposure on experimental skin flaps. Plast Reconstr Surg 1985;75:544-51.

6. Craig S, Rees TD. The effects of smoking on experimental skin flaps in hamsters. Plast Reconstr Surg 1985;75:842-6.

7. Rees TD, Liverett DM, Guy CL. The effect of cigarette smoking on skin-flap survival in the face lift patient. Plast Reconstr Surg 1984;73:911-5.

8. Riefkohl R, Wolfe JA, Cox EB, McCarthy KS. Association between cutaneous occlusive vascular disease, cigarette smoking, and skin slough after rhytidectomy. Plast Reconstr Surg 1986;77:592-5.

9. Goldminz D, Bennett RG. Cigarette smoking and flap and full-thickness graft necrosis. Arch Dermatol 1991;127: 1012-5.

10. Lovich SF, Arnold PG. The effect of smoking on muscle transposition. Plast Reconstr Surg 1994;93:825-8.

11. Tsur H, Daniller A, Strauch B. Neovascularization of skin

flaps: route and timing. Plast Reconstr Surg 1980;66:85-93.

12. Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science 1983;221:1283-5.

13. Hunt TK, Pai MP. Effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet 1972;135:561-7.

14. Hunt TK, Linsey M, Sonne M, Jawetz E. Oxygen tension and wound infection. Surg Forum 1972;23:47-9.

15. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic: the effect of inspired oxygen on infection. Arch Surg 1984; 119:199-204.

16. Jensen JA, Goodson WH, Hopf HW, Hunt TK. Cigarette smoking decreases tissue oxygen. Arch Surg 1991;126:1131-4.

17. McBride PE. The health consequences of smoking. Cardiovascular diseases. Med Clin North Am 1992;76:333-53.

18. Nowak J, Murray JJ, Oates JA. Biochemical evidence of a chronic abnormality in platelet and vascular function in healthy individuals who smoke cigarettes. Circulation 1987;76:6-14.

19. Davies JM, Platto IP, Jones JG, Veale A, Wardrop CAJ. Effect of stopping smoking for 48 hours on oxygen availability from the blood: a study of pregnant women. BMJ 1979;2:355-6.

* * *

OTOPLASTY AND RECONSTRUCTION OF AURICULAR DEFECTS

The International Course on Otoplasty and Reconstruction of Auricular Defects will be held in Lübeck, Germany, March 21-22, 1999. For information, contact PD Dr Dr R. Siegert/M. Haase, Department of Otorhinolaryngology and Head and Neck Plastic Surgery, Medical University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany; telephone +49-451-500-3189; fax +49-451-500-4192; e-mail: Sigert@medinf.mu-luebeck.de.

Ann Otol Rhinol Laryngol 108:1999

AUTOTRANSPLANTATION OF THE TRACHEA: EXPERIMENTAL EVALUATION OF A RECONSTRUCTIVE TECHNIQUE FOR EXTENDED HEMILARYNGECTOMY DEFECTS

PIERRE R. DELAERE, MD, PHD
VINCENT VANDER POORTEN, MD, MSC ROBERT HERMANS, MD
LEUVEN, BELGIUM

Vascularized segments of trachea were used to repair extended hemilaryngectomy defects in a rabbit model. The cervical trachea was revascularized in a first stage by a fascia flap. In a second stage, the cervical trachea was isolated and transformed into a patch that could be autotransplanted on a vascular carrier. The patches were used for the reconstruction of hemilaryngectomy defects including half of the cricoid. Two months after transplantation, the vascular and morphologic characteristics of the tracheal patches were examined with silicone dye angiography and magnetic resonance imaging. The tracheal patches showed a reliable blood supply when wrapped in vascularized fascia. The patches provided a functional reconstruction of hemicricolaryngectomy defects. It is concluded that autotransplantation of the trachea should be further explored as a potential means for extending the limits of conservation laryngeal surgery.

KEY WORDS — autograft, larynx, patch, reconstruction, revascularization, trachea.

INTRODUCTION

A major limitation on the extent of partial laryngeal resections is that nearly all the conservation procedures are intended for tumors that may be resected without violation of the cricoid cartilage. In many cases, a rational ablation for a T3 glottic cancer removes, at least on the tumor side, the paraglottic space and its contiguous structures, including the cricoid and thyroid cartilages. The remaining larynx consists then of 1 thyroid ala with the corresponding true vocal cord and half of the cricoid with 1 mobile arytenoid. These tissues may theoretically fulfill all laryngeal functions if the morphology of the resected hemilarynx can be restored. Reliable reconstructive tissues allowing cricoid reconstruction are, however, not available, so that total laryngectomy becomes the only option in most T3 glottic tumors.

It can be anticipated that the limits of partial laryngectomy could be extended if reliable reconstructive methods for hemicricolaryngectomy defects were available. Optimal repair tissues should make use of a vascularized mucosal lining that allows primary healing and of a supportive cartilaginous framework that provides posterior glottic bulk and immediate airway support at the subglottic level. Only the larynx and trachea are potential donor sites fulfilling this combination of tissue requirements. Because allotransplantation of laryngeal tissue is at this moment not practical due to the need for continuous immunosuppression, autologous donor sites have to be fully explored.

Autologous laryngeal tissues that may be used for reconstruction are of limited quantity. The epiglottis may be moved downward in the repair of anterior laryngeal defects,[1] and the supraglottic thyroid cartilage with its mucosa may be mobilized inferiorly in some cases of imbrication laryngectomy.[2] These possibilities are of no use to larger laryngeal defects including half of the cricoid.

The purpose of this research was to examine whether the trachea could be used as an alternative donor site for extended laryngeal repair. Tracheal resection with reanastomosis demonstrated that half of the trachea may be removed.[3] We assumed that similar segments of trachea might be used for laryngeal reconstruction if they could be transformed into viable transferable patches. We developed an animal model of hemicricoid reconstruction to test this hypothesis.

Previous research in rabbits has shown that tracheal allografts and autografts can be revascularized by vascular induction through the intercartilaginous and membranous ligaments.[4,5] The trachea is therefore wrapped, after circumferential mobilization, by a thin, axially perfused fascia flap to promote angiogenesis between flap and trachea (Fig 1). The revascularized trachea may be isolated and transplanted

---

From the Departments of Otorhinolaryngology–Head and Neck Surgery (Delaere, Vander Poorten) and Radiology (Hermans), University Hospitals of Leuven, Leuven, Belgium.

CORRESPONDENCE — Pierre R. Delaere, MD, PhD, Dept of Otorhinolaryngology, University Hospital St Rafael, KU Leuven, Kapucijnenvoer 33, B-3000 Leuven, Belgium.

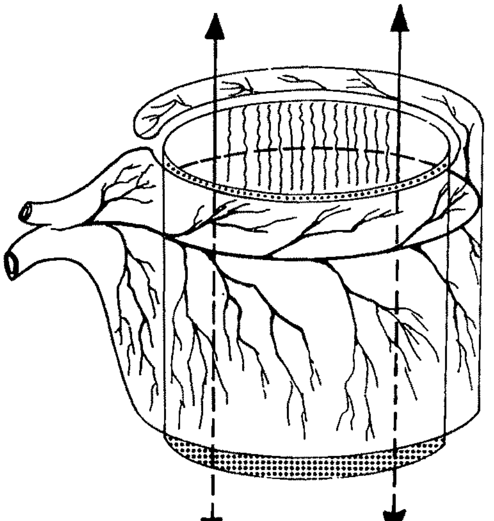


Fig 1. Schematic representation of tracheal revascularization. Cervical trachea is mobilized and circumferentially wrapped by vascularized fascia. After revascularization, membranous trachea is excised (arrows) to obtain tracheal patch that is fully supported by cartilage.

on its fascial blood supply after a staging period of 14 days.

Tracheal autografts were revascularized orthotopically and transformed into patches useful for reconstruction of hemilaryngectomy defects including half of the cricoid.

MATERIAL AND METHODS

Vascular Induction of Tracheal Autografts. Twelve mature New Zealand White rabbits, with a mean age of 6 months and weighing between 3 and 3.5 kg, were used. The animals were premedicated with 0.3 mL/kg of Hypnorm intramuscularly, and anesthesia was maintained with halothane through mask ventilation. The left thoracic skin was incised and the left lateral thoracic fascia flap was isolated on the lateral thoracic vessels. The anatomy and dissection technique of this axial perfused fascia flap were described previously.[4] The cervical trachea was reached through a midline neck incision. The upper end of the cervical trachea was dissected over 2 cm from the underlying esophagus and cleared from most of the connective tissue without incising the trachea. The lateral thoracic fascia flap was subcutaneously rotated to the neck region. The cervical trachea was wrapped by the transposed lateral thoracic fascia flap (Fig 1).

Transformation of Revascularized Trachea Into Tracheal Patch. After 14 days of vascular induction, the rabbits were premedicated and anesthetized with inhaled halothane and oxygen through mask ventilation. The neck was reopened and the cervical trachea, wrapped by the fascial flap, was isolated from the airway. The fascial flap was incised longitudinally at the distal site of the fascial flap, and the membranous part of the isolated tracheal segment was excised (Fig 1). Full cartilaginous supported patches of 2 × 1.3 cm, pedicled on the lateral thoracic artery and vein, were obtained. At this stage, 2 animals underwent angiography to ascertain mucosal patch viability and to ascertain the effectiveness of the vascular induction technique. For the intermediate silicone dye angiographies, the left axillary region was opened, and the left thoracic artery was cannulated with a 14-gauge catheter. The vasculature was flushed through the cannula with 10 mL of heparinized normal saline solution (10 IU of heparin per milliliter) followed by 5 mL of blue silicone dye (Microfil; Canton Bio-Medical Products Inc, Boulder, Colo). The mucosal surface area that showed a blue coloration by the silicone dye was used as a measure for patch viability.

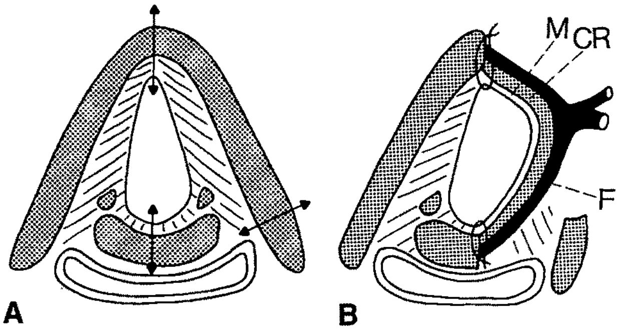


Fig 2. Schematic representation of tracheal autotransplantation on axial images. A) Resection (arrows) includes left thyroid cartilage, left half of cricoid, and left arytenoid. B) Reconstruction with tracheal patch pedicled on left thoracic fascia flap. Patch consists of 3 layers: mucosa (M), cartilage ring (CR), and fascia (F).

Reconstruction of Hemilaryngectomy Defects. The remaining 10 animals underwent a hemilaryngectomy including the left thyroid cartilage, the left half of the cricoid, and the left arytenoid. This defect was reconstructed with the tracheal patch pedicled on the left thoracic fascial flap (Fig 2). The transplant was oriented in its original proximal-distal direction to allow for mucociliary clearance over the transplanted region. The anastomosis between the posterior cricoid and the tracheal patch was done first with interrupted polypropylene (Prolene 6.0, Ethicon) sutures. The bulk at the arytenoid region was restored, and hypopharyngeal mucosa was sutured over the upper dorsal edge of the patch. The laryngeal reconstruction was completed by suturing the tracheal patch anteriorly and superiorly into the laryngeal defect. Laryngotracheal continuity was repaired by an upward tracheal mobilization and reanastomosis between the trachea and the reconstructed caudal cri-

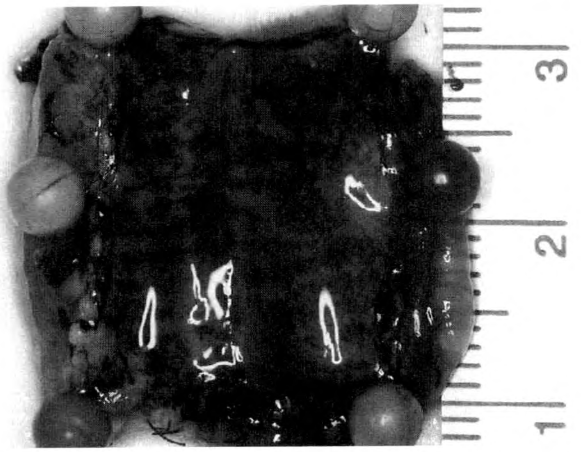


Fig 3. Tracheal patch after intermediate silicone dye angiography. Darker areas of patch are silicone-injected submucosal vessels perfused by fascia. Vessels penetrating intercartilaginous ligaments are clearly visible.

coid cartilage (Prolene 5.0, Ethicon). All sutures were placed with the knots tied on the outside. The animals breathed spontaneously during the entire operation, and no tracheotomy or intraluminal stent was placed.

Magnetic resonance imaging examinations were performed 8 weeks after reconstruction. A high-resolution, gadolinium-enhanced, T1-weighted spin echo sequence was used to obtain a magnetic resonance study in the axial plane from the transplanted region. The reconstructions were evaluated morphologically shortly after the magnetic resonance studies and after silicone dye infusion of the vascular fascial pedicle. After these injections were completed, the animals were painlessly killed by a lethal intramuscular injection of sodium pentobarbital. The larynges were removed and they were axially cut for macroscopic evaluation. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the US National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the US National Institutes of Health.

RESULTS

Intermediate Silicone Dye Angiography. Perfusion of the tracheal patch by the fascia flap was evaluated after isolation and disruption of the native tracheal vascularization and after excision of the membra-

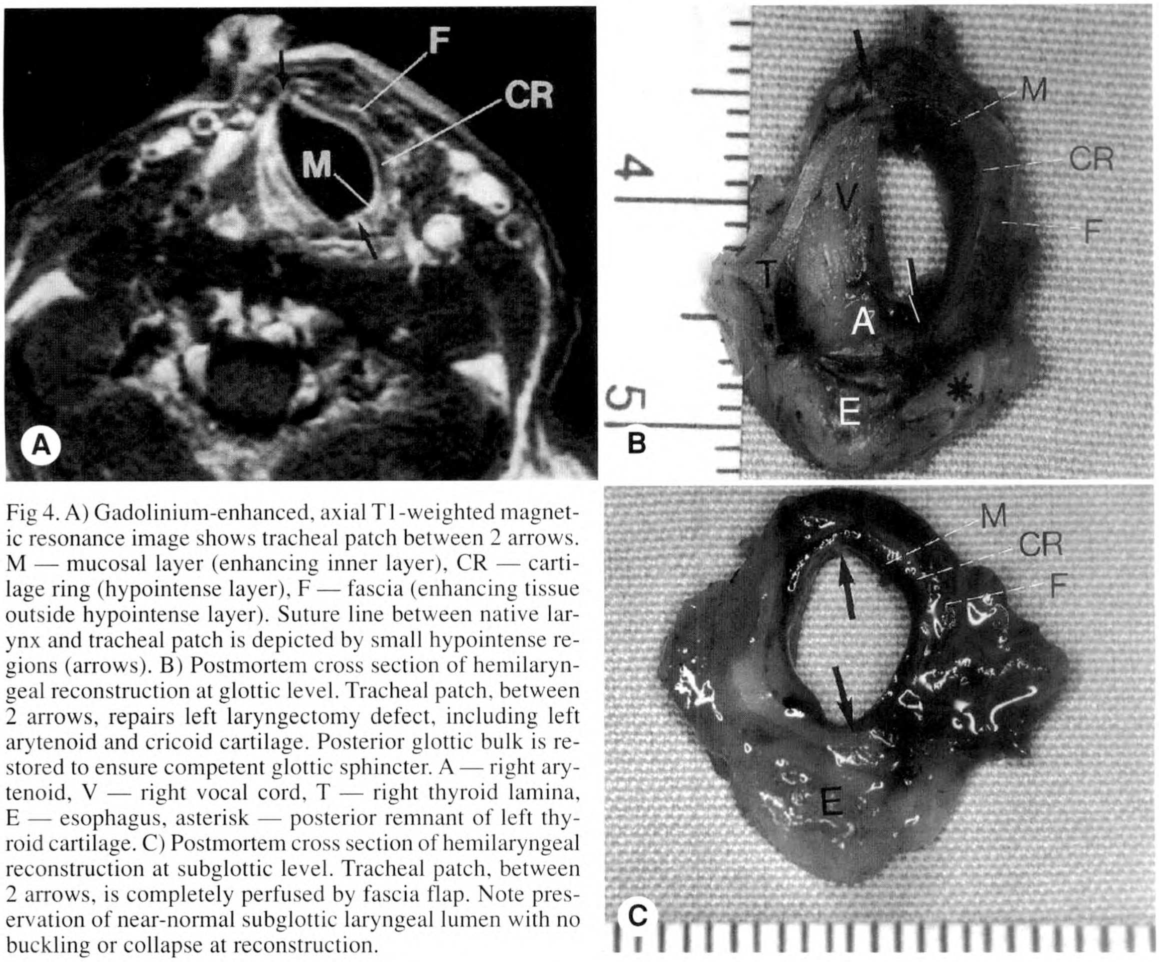


Fig 4. A) Gadolinium-enhanced, axial T1-weighted magnetic resonance image shows tracheal patch between 2 arrows. M — mucosal layer (enhancing inner layer), CR — cartilage ring (hypointense layer), F — fascia (enhancing tissue outside hypointense layer). Suture line between native larynx and tracheal patch is depicted by small hypointense regions (arrows). B) Postmortem cross section of hemilaryngeal reconstruction at glottic level. Tracheal patch, between 2 arrows, repairs left laryngectomy defect, including left arytenoid and cricoid cartilage. Posterior glottic bulk is restored to ensure competent glottic sphincter. A — right arytenoid, V — right vocal cord, T — right thyroid lamina, E — esophagus, asterisk — posterior remnant of left thyroid cartilage. C) Postmortem cross section of hemilaryngeal reconstruction at subglottic level. Tracheal patch, between 2 arrows, is completely perfused by fascia flap. Note preservation of near-normal subglottic laryngeal lumen with no buckling or collapse at reconstruction.

nous trachea with disruption of the fascial blood supply through the dorsal, membranous part. The macroscopic evaluation of the mucosal surface of the tracheal patch after 14 days of vascular induction showed an extensive arborizing network of small vessels injected with blue silicone rubber. The blood supply of the isolated tracheal patch was provided by the fascial vascular pedicle through the intercartilaginous ligaments. The blood supply was observed over the complete mucosal surface area of the patch and was sufficient to allow a viable transplantation of the tracheal patch (Fig 3).

Morphologic Evaluation of Reconstructed Hemilaryngeal Defects. Two animals died immediately postoperatively because of accumulation of blood inside the airway. Eight survived the follow-up period and had normal respiration and swallowing.

On magnetic resonance imaging (Fig 4A), an enhancing inner layer with luminal concavity allowed easy identification of the reconstructed hemilarynx. A hypointense layer was observed just outside the enhancing layer, and enhancing tissue was seen wrapped around the reconstruction.

On postmortem macroscopic evaluation (Fig 4B, C), the mucosal lining of the patch and the fascia flap were uniformly colored by the blue silicone dye. The blood supply of the tracheal autograft completely originated from the lateral thoracic vascular pedicle. Matching of the macroscopic preparations with the magnetic resonance images showed that the inner enhancing layer bordering the lumen corresponded to the mucosal layer of the tracheal patch; the hypointense layer outside the submucosa of the tracheal patch related to the tracheal cartilaginous component. The enhancing tissue layer wrapped around the tracheal patch corresponded to the vascularized fascia flap.

DISCUSSION

A new concept of "tracheal autotransplantation" is presented to re-form the posterior vertical height of the cricoid and the diameter of the airway lumen after hemilaryngectomy with hemicricoid resection. Transplantation of a patch consisting of the cartilaginous trachea is possible because its blood supply may be fully provided by a fascia flap after a 14-day period of progressive revascularization. Because the cartilage rings of the patch do not allow vessel ingrowth, the mucosal lining of the patch has to survive transplantation by the vascular connections reaching the mucosa through the intercartilaginous ligaments.

Patch tracheal autotransplantation allowed for repair of full hemicricoid defects with preservation of the tissue bulk at the arytenoid region. This tissue reconstruction ensured a patent airway and competent glottic sphincter function. A patent airway was maintained by the cartilaginous support provided by the tracheal rings and by the mucosal lining, which ensured primary wound healing and mucociliary clearance activity. It has been shown experimentally that the mucosal lining of the trachea preserves its mucociliary clearance function after transplantation in the original proximal-distal direction.[5] Aspiration was prevented by maintaining the functional integrity of the posterior third of the glottis. This was accomplished by preserving 1 arytenoid while reconstructing the resected arytenoid and cricoid with the tracheal patch.

It can be concluded that autotransplantation of revascularized tracheal patches allows for reconstruction of extended hemilaryngeal defects in rabbits without the morbidity related to a tracheostomy or a laryngeal stent. The patch vascularity, the respiratory mucosa, and the full cartilaginous patch support are responsible for the reliability of the technique. This concept challenges the current statement that the cricoid cartilage needs preservation to allow for decannulation after reconstruction. The trachea autotransplantation technique should be further explored as a means for extending the limits of conservation laryngeal surgery.

REFERENCES

1. Tucker HM, Wood BG, Levine H, Katz R. Glottic reconstruction after near total laryngectomy. Laryngoscope 1979;89:609-18.

2. Liu C, Ward PH, Pleet L. Imbrication reconstruction following partial laryngectomy. Ann Otol Rhinol Laryngol 1986;95:567-71.

3. Grillo HC. Tracheal reconstruction. Indications and techniques. Arch Otolaryngol 1972;96:31-9.

4. Delaere PR, Liu ZY, Hermans R, Sciot R, Feenstra L. Experimental tracheal allograft revascularization and transplantation. J Thorac Cardiovasc Surg 1995;110:728-37.

5. Delaere PR, Liu ZY, Delanghe G, Gyselen K, Jorissen M, Feenstra L. Mucociliary clearance following segmental tracheal reversal. Laryngoscope 1996;106:450-6.

Ann Otol Rhinol Laryngol 108:1999

TRANSNASAL ENDOSCOPIC REMOVAL OF AN ORBITAL CAVERNOMA

PHILIPPE HERMAN, MD, PHD
GUILLAUME LOT, MD
BÉNÉDICTE SILHOUETTE, MD
RÉMI MARIANOWSKI, MD
FRÉDÉRIC PORTIER, MD
MICHEL WASSEF, MD
PATRICE TRAN BA HUY, MD
PARIS, FRANCE

The approach to posterior and medial orbital tumors is still a challenge, since poor functional results are frequent. We report a case of cavernoma successfully removed by a modified transnasal endoscopic procedure. The patient, a 56-year-old woman, complained of a decrease in vision of the left eye. Magnetic resonance imaging evidenced a lesion in the posterior part of the orbital cavity, inferior to the optic nerve, extending to the sphenoidal cleft. The lesion was isodense on T1-weighted images and showed contrast enhancement. Because of the medial location of the tumor, the patient was referred to the otolaryngology department by the neurosurgeons, and a transnasal endoscopic approach was chosen. A large exposure of the operative field was obtained, and a cavernoma was removed. Rapid relief of the symptoms was obtained. In view of this good result, we advocate the transnasal endoscopic approach in cases of inferomedial and posterior intraconal lesions as an alternative and addition to the standard techniques of orbital surgery.

KEY WORDS — cavernoma, endoscopic surgery, minimally invasive surgery, orbit.

INTRODUCTION

Surgical treatment of orbital tumors remains a formidable challenge due to the complexity of cranio-orbital anatomy and the diversity of tissue types. Because the orbit is intimately related to the anterior, middle cranial, and infratemporal fossae, the cavernous sinus, and the paranasal sinuses, various surgical approaches have been developed.[1] However, the approach to posterior and medial intraconal lesions is still difficult. Any lateral approach seems inappropriate, since the operative route would be obstructed not only by the optic nerve, but also by intraorbital vessels and cranial nerves. Subfrontal or pterional approaches also make it difficult to maintain the functional integrity. Finally, transconjunctival medial orbitotomy is not possible in the case of posterior lesions.

We report a case of orbital tumor that was successfully removed by a modified transnasal endoscopic procedure. This is, to the best of our knowledge, the first report of surgical removal of an orbital tumor by a transnasal endoscopic approach. This technique might be recommended in selected cases, when the location and the type of tumor dictate the inferior or medial approach.

CASE REPORT

A 56-year-old woman complained of a progressive decrease in vision of the left eye. Physical examination revealed a slight decrease of visual acuity (20/25), a moderate proptosis (3 mm), and a symmetric hyperopia (+2.5 on each side). Visual field examination revealed a diminished macular threshold test result on the left side with a concentric reduction of the peripheral vision field and an enlargement of the blind spot. The ocular fundus was normal.

A computed tomography scan revealed the presence of a well-circumscribed, 10-mm-diameter mass at the medial and posterior part of the left orbit (Fig 1). The mass was continuous with the medial rectus muscle and reached the sphenoidal cleft, but remained distinct from the optic nerve. There was no thickening of bone, as in the case of a meningioma, but rather, a thinning and deformation of the external wall of a posterior ethmoidal cell reaching the sphenoethmoidal plate. Magnetic resonance imaging evidenced an 11 × 8 × 12-mm lesion in the posterior part of the orbital cavity, extending to the sphenoidal cleft. The lesion was isodense on T1-weighted images and showed moderate contrast enhancement (Fig 1). It seemed intraconal, inferior to the optic nerve. This was suggestive of a neurinoma of the ophthalmic branch of the fifth cranial nerve.

Because of the medial, as well as posterior, situation of the lesion, the patient was referred to the otolaryngology department by the neurosurgeons. A direct route by a transnasal endoscopic approach was

---

From the Departments of Otolaryngology (Herman, Marianowski, Portier, Tran Ba Huy), Neurosurgery (Lot, Silhouette), and Pathology (Wassef), Hôpital Lariboisière, Paris, France.

CORRESPONDENCE — Philippe Herman, MD, PhD, Hôpital Lariboisière, Service ORL, 2, rue Ambroise Paré, 75010 Paris, France.

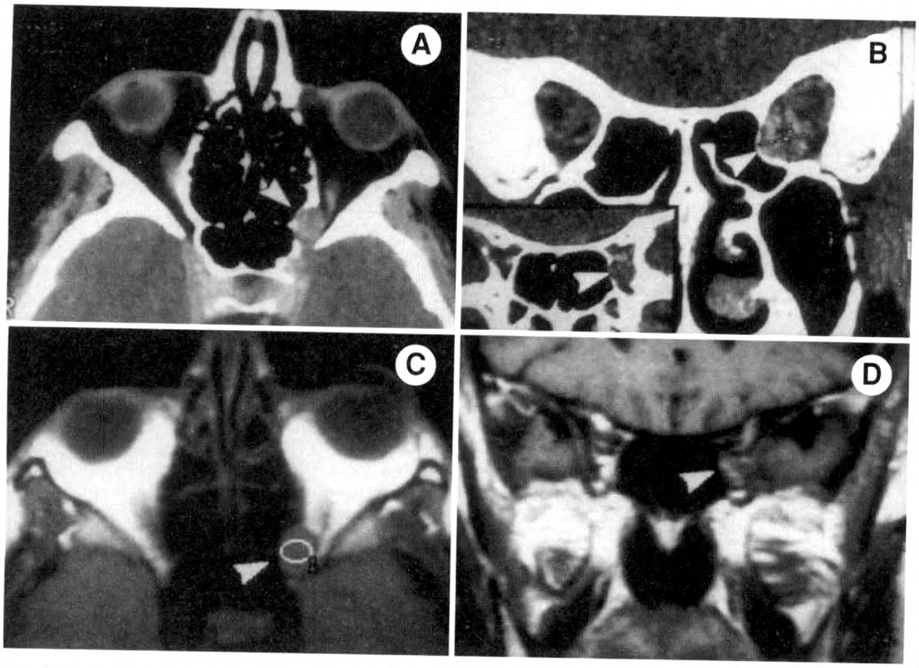


Fig 1. Preoperative imaging data. Arrowheads — lesion. A,B) Axial computed tomography. A) Well-marginated lesion medial to optic nerve. B) Thinning of medial wall of orbit. Inset) Extension of lesion to orbital apex. C,D) T1-weighted magnetic resonance imaging. C) Isodense lesion. D) Mild contrast enhancement.

chosen in an attempt to preserve functional integrity.

SURGICAL PROCEDURE

After an ethmoidectomy, a large sphenoidotomy was performed to provide a complete exposure of the external wall of the sphenoid sinus. A blue area corresponding to the lesion was seen inferior to the canal of the optic nerve, at the insertion of the ethmoidosphenoidal plate (Fig 2). The medial wall of the orbit was removed with a diamond drill under irrigation. After incision of the orbital periosteum, a biopsy specimen of the tumor was taken. Frozen section examination was suggestive of a vascular and benign lesion. The tumor was carefully dissected from the orbital fat, taking care not to injure the exposed rectus muscle (Fig 3). A spheric encapsulated tumor was completely removed. A silicone sheet was then applied on the orbital fat, and the ethmoid cavity was filled with ointment. Histologic examination revealed a cavernous hemangioma[2,3] composed of large, dilated, interconnecting vascular channels separated by fibrous septae with pseudopapillary structures (Fig 4). Endoscopic cleaning of the cavity was performed weekly for 1 month. Follow-up remained uneventful except for an acute orbititis that occurred during healing of the ethmoid cavity and resolved with antibiotics. Six months after surgery, a complete ophthalmologic examination was performed. It evidenced the disappearance of proptosis and the recovery of visual acuity and of the visual field. A computed tomography scan evidenced the complete disappearance of the lesion.

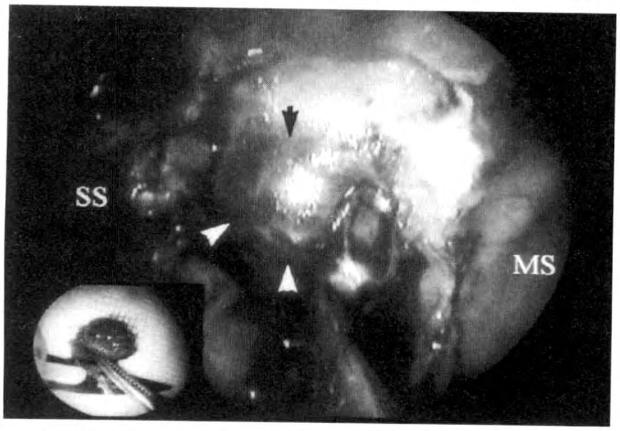


Fig 2. Operative field. Internal wall of orbit was thinned with diamond drill at junction of sphenoid sinus (SS), ethmoid sinus, and maxillary sinus (MS). Arrow and arrowheads point to tumor, which prolapsed into sinus. Inset) Encapsulated lesion after removal.

DISCUSSION

This is, to the best of our knowledge, the first re-

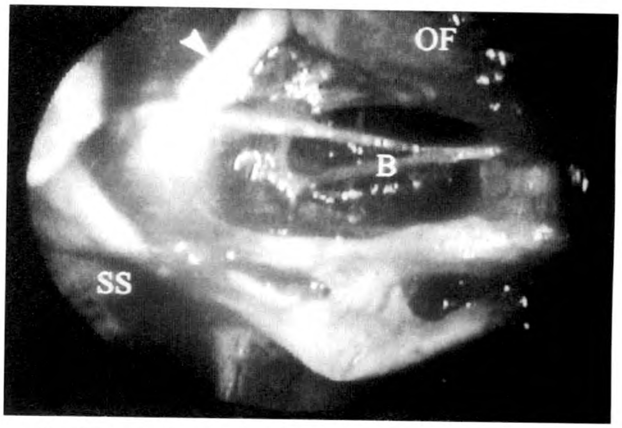


Fig 3. Orbital contents. After dissection of lesion from orbital fat (OF), tumor bed (B) was next to tendon of rectus muscle (arrowhead). SS — sphenoid sinus.

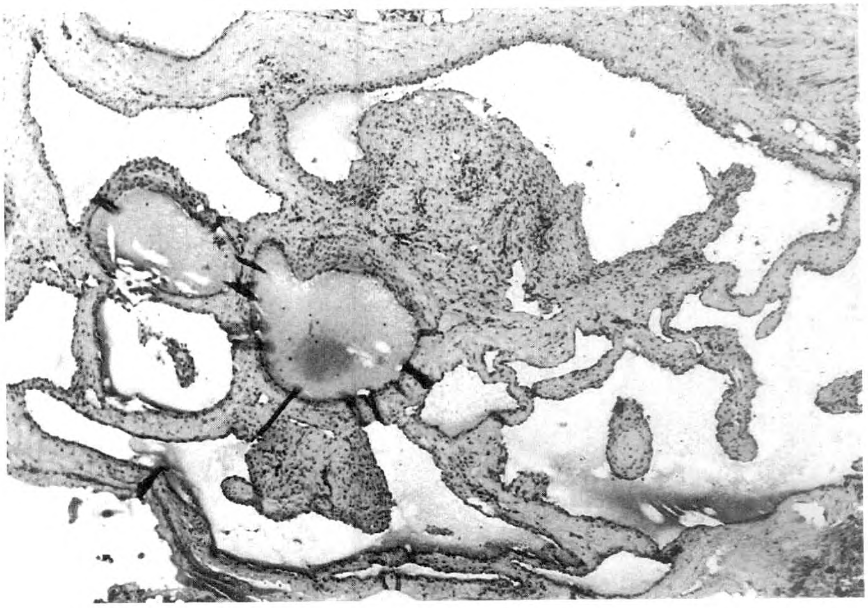


Fig 4. Histologic features of lesion (hematein-eosin-saffron, original ×40). Dilated vascular channels are separated by fibrous septae.

port of surgical removal of an orbital tumor by a transnasal endoscopic approach. Cavernous hemangioma, the most common benign orbital tumor,[4] is a low-flow lesion that affects mostly adults. The typical location of the tumor is anterior: it usually spares the triangular orbital apex. The onset of symptoms is gradual, starting with a progressive, well-tolerated, and reducible proptosis, diplopia being usually absent or minimal. The imaging pattern is almost diagnostic. Computed tomodensitometry shows a well-defined round or oval mass in the muscle cone with variable but constant enhancement. The lesion is isointense with the brain on T1-weighted sequences and hyperintense on T2-weighted magnetic resonance images. In this observation, the very posterior location of the tumor, which resulted in an early decrease in vision, was unusual for a cavernous hemangioma and suggested either a neurinoma or another benign mesenchymal lesion.

The surgical approach to orbital tumors must provide maximum safety and optimal visualization. Surgical approaches to the orbit can be described as anterior, superior, medial, lateral, and inferior.[1] The choice of the approach depends on the location within the orbit and the relationship with the adjacent structures. However, Missori et al[5] have highlighted the significant morbidity associated with the removal of these tumors when they are close to the apex. In those cases, a pterional approach to the contralateral orbit has been advocated,[6] which seems an extreme procedure for an orbital lesion. The medial approach, usually performed by an external incision, allows access to the medial orbital contents, as well as the ethmoid labyrinth, sphenoid sinus, and optic nerve.[7] In the last decade, an endoscopic technique has been recommended as a useful procedure for decompressing the orbit in the case of dysthyroid orbitopathy,[8] either as a single procedure or combined with a lateral approach.[9] Briefly, after a complete endonasal ethmoidectomy, the lamina papyracea is removed from the lacrimal bone anteriorly, back to the optic canal. The medial part of the orbital floor is then resected, and longitudinal incisions in the periorbita are made as originally described by Walsh and Ogura.[10] However, there is no report concerning this approach for the removal of orbital tumors. This may result from the attitude of physicians: orbital tumors are most often referred to neurosurgeons, for whom the endoscopic approach through the sinus might be unfamiliar. It seems a modern alternative to the contralateral pterional transsphenoidal-transethmoidal route in the case of an unusual posterior and medial tumor location.[6] Further, the functional result we obtained is promising, since the prognosis of preoperative impaired visual function is unfavorable.[5]

It should be pointed out that the possibility of dissection in the orbit is limited with this endoscopic approach, especially for intraconal lesions. Therefore, this procedure should be recommended only when careful analysis of the imaging data predicts an easy dissection, which depends on the location, which should be medial or inferior, and on the type of tumor, which is predicted by noninvasive techniques in more than 95% of cases.[11] Finally, the inferomedial posterior location is rare and represents 2 of 80 orbital lesions in the series of Hassler et al,[6] and 2 of 30 in the series of cavernomas that were treated at our institution from 1986 to 1996 (unpublished observation).

In view of this excellent functional result, we advocate the transnasal endoscopic approach in rare cases of inferomedial and posterior intraconal lesions as an alternative and addition to the standard techniques of orbital surgery.

REFERENCES

1. Bumpous J, Janecka IP. Transorbital approaches to the cranial base. Clin Plast Surg 1995;22:461-81.
2. Enziger FM, Weiss SW. Soft tissue tumors. 3rd ed. St Louis, Mo: Mosby, 1995.
3. Wassef M. Angiomes et malformations vasculaires cervico-céphaliques. Aspects histo-pathologiques et classification. J Mal Vasc 1992;17:20-5.
4. Reese AG. Tumors of the eye. 3rd ed. Hagerstown, Md: Harper and Row, 1976.
5. Missori P, Tarantino R, Delfini R, Lunardi P, Cantore G. Surgical management of orbital cavernous angiomas: prognosis for visual function after removal. Neurosurgery 1994;35:34-7.
6. Hassler WE, Meyer B, Rohde V, Unsöld R. Pterional approach to the contralateral orbit. Neurosurgery 1994;34:552-4.
7. Janecka IP. Classification of facial translocation approach to the skull base. Otolaryngol Head Neck Surg 1995;112:579-83.
8. Kennedy DW, Goostein ML, Miller NR. Endoscopic transnasal orbital decompression. Arch Otolaryngol Head Neck Surg 1990;116:275-82.
9. Jorissen M, Feenstra L. Dysthyroid orbitopathy and orbital decompression. A review. Acta Otorhinolaryngol Belg 1992;46:303-9.
10. Walsh TE, Ogura JH. Transantral orbital decompression for dysthyroid orbitopathy. Laryngoscope 1957;67:544-68.
11. Char DH. Management of orbital tumors. Mayo Clin Proc 1993;68:1081-96.

≈

ADVANCED EAR SURGERY

A Compact Training Course in Advanced Ear Surgery (Endaural Tympano-meatoplasty and Enlarged Middle Fossa Approach) will be held May 16-19, 1999, in Erlangen-Nuremberg, Germany. For information, contact Prof Dr M. E. Wigand, Dept of ORL, University of Erlangen-Nuremberg, HNO Universitatsklinik, Waldstrasse 1, D-91054, Erlangen, Germany; telephone +49/9131/85-3141; fax +49/9131/85-6857.

Ann Otol Rhinol Laryngol 108:1999

PATIENTS WITH CHARGE ASSOCIATION: A MODEL TO STUDY SACCULAR FUNCTION IN THE HUMAN

JEAN-PHILIPPE GUYOT, MD
GENEVA, SWITZERLAND

DOMINIQUE VIBERT, MD
BERNE, SWITZERLAND

The term CHARGE association refers to a combination of congenital malformations, the mnemonic CHARGE designating the most frequently occurring anomalies in the constellation. "C" indicates coloboma of the retina, "H" heart defects, "A" choanal atresia, "R" retarded growth and/or central nervous system anomalies, "G" genital hypoplasia, and "E" ear anomalies and/or deafness. The inner ear anomaly consists of a specific form of labyrinthine dysplasia that includes Mondini dysplasia of the pars inferior (cochlea and saccule) and complete absence of the pars superior (utricle and semicircular canals). We observed the development of a child with CHARGE association up to the age of 10 years. There was complete absence of nystagmic response to bithermal caloric and rotatory pendular stimuli. A nystagmic reaction was elicited by the off-vertical axis rotation test, indicating stimulation of the saccular macula, the sole remaining vestibular sense organ in this dysplasia. This reaffirms that the saccule is a vestibular organ, even though it is located in the pars inferior. In spite of the severe bilateral vestibular deficit and coloboma of the retina, the child was able to walk at the age of 2 years. The delay in the development of walking was not due to central nervous system anomalies, as suggested by the "R" of the acronym CHARGE, but rather, to the severe sensorineural visual and vestibular deficits.

KEY WORDS — development, inner ear anomalies, saccule, vestibular deficit.

INTRODUCTION

In 1981, the term CHARGE association was introduced by Pagon et al[1] to describe patients suffering from a combination of various congenital anomalies. CHARGE is a mnemonic designating the most frequently occurring anomalies observed in this constellation, "C" indicating coloboma of the retina, "H" congenital heart defects, "A" choanal atresia, "R" retarded growth and development and/or central nervous system (CNS) anomalies, "G" genital hypoplasia, and "E" ear anomalies and/or deafness. Other anomalies may coexist, such as facial palsy, micrognathia, cleft palate, laryngotracheal abnormalities, and/or tracheoesophageal fistula. Choanal atresia and/or ocular coloboma and at least 4 of the principal anomalies must be present to characterize the syndrome.[1]

In 1986[2] and 1987,[3] 2 publications reported the temporal bone anomaly in CHARGE association. Both descriptions included complete absence of the pars superior (bony and membranous semicircular canals and utricle) and a Mondini dysplasia of the cochlea with preservation of the saccule and its innervation. In a review of the literature, Guyot et al[3] found 4 previous reports of this unusual form of dysplasia. It was first reported by Fraser[4] in 1927. Subsequent cases were reported by Paparella and el-Fiky[5] in 1972, Sekhar and Sachs[6] in 1976, and Paparella[7] in 1980. In all cases, the anomalies of the temporal bone were associated with multiple other congenital defects, retrospectively appearing consistent with a diagnosis of CHARGE association.[3] Therefore, Guyot et al[3] suggested that the temporal bone anomalies represent a specific form of labyrinthine dysplasia that could be conveniently called CHARGE dysplasia.

The off-vertical axis rotation (OVAR) test is a newly developed method to evaluate the function of otolithic organs[8-10] that consists of recording the nystagmic response during a constant-velocity rotation around a tilted axis. Several experimental studies have shown that the nystagmic response to OVAR is otolithic in origin and is not modified by a canal occlusion,[11,12] but is abolished after bilateral vestibular neurectomy.[12]

Recently, we had the opportunity to observe the development of a child with CHARGE association up to the age of 10 years. At the age of 8 years, he was cooperative enough to undergo diverse vestibular function tests. No nystagmus was elicited by canal stimulations, but a nystagmic response was induced by the OVAR. Since the utricle is absent in CHARGE dysplasia,[2,3] it is logical to assume that this response was saccular in origin.

CASE REPORT

The patient was born full-term, weighing 3.38 kg,

From the Department of Otolaryngology–Head and Neck Surgery, University Hospital, Geneva (Guyot), and the University Clinic of ENT–Head and Neck Surgery, Inselspital, Berne (Vibert), Switzerland. This work was supported by the Swiss National Research Foundation (grant FNRS No. 32-35594-92).

CORRESPONDENCE — Jean-Philippe Guyot, MD, Dept of Otolaryngology, University Hospital, 1211 Geneva 14, Switzerland.

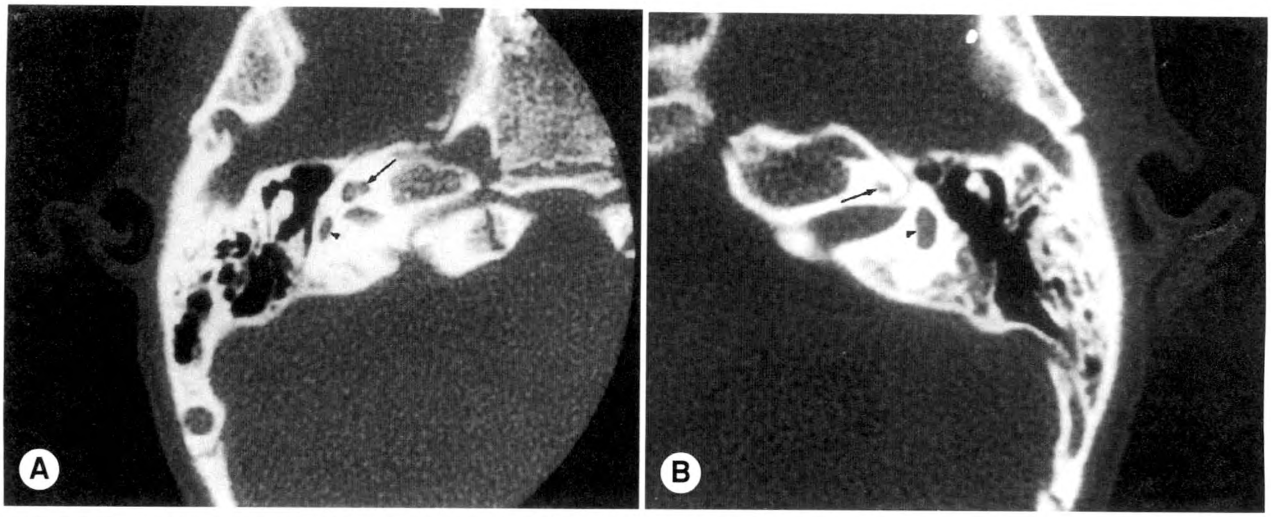


Fig 1. Computed tomograms of temporal bones of child suffering from CHARGE association. Both temporal bones showed Mondini dysplasia of cochlea (arrow), large vestibule (arrowhead), and absence of 3 semicircular canals. A) Right ear. B) Left ear.

to a gravida 1, para 0, 22-year-old woman with a normal prenatal history. At birth, examination of the child revealed bilateral coloboma of the retina, microphthalmia and microcornea, a convergent strabismus of the left eye, right choanal atresia, genital hypoplasia and bilateral cryptorchidia, a deformed and low-set right pinna, and a right hemifacial microsomia and facial palsy. There was no heart defect or CNS anomaly. A chromosome analysis showed a normal karyotype. The child grew and progressed normally except for a delay in walking. He was able to walk freely at the age of 2 years.

He was referred to us at the age of 5 years for surgical repair of the right choanal atresia. A computed tomography (CT) scan of the head demonstrated right bony choanal atresia and typical features of CHARGE dysplasia of both temporal bones (Fig 1). Short- and middle-latency auditory evoked potentials showed a bilateral low- and high-frequency hearing loss. One year later, it was possible to assess the hearing with a pure tone audiogram that confirmed a mixed conductive and sensorineural bilateral hearing loss (Fig 2).

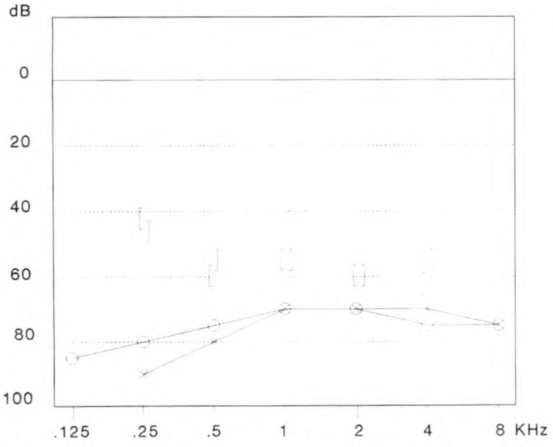


Fig 2. Hearing thresholds at age of 6 years. [— right bone conduction;] — left bone conduction; ○ — right air conduction; × — left air conduction.

At 8 years, vestibular function was assessed with electronystagmography. The pendular rotatory test (undamped rotation, 360° in 20-second intervals, 0.05-Hz frequency, and in 10-second intervals, 0.2-Hz frequency) and caloric stimulation at 44°C, 30°C, and 10°C elicited no nystagmic response. The nystagmic response to optokinetic stimulation (whole-field rotation at speeds of 25°/s, 50°/s, and 75°/s) was normal. Voluntary saccadic and smooth pursuit eye movements were altered.

The OVAR test was performed at the Otoneurological Unit of the University Clinic of ENT–Head and Neck Surgery in Berne (Switzerland), by means of a prototypical system. The details of the testing procedure have been reported previously.[9,10,13] Briefly, the test is performed in darkness with the subject firmly fastened to an armchair with eyes opened. The paradigm consists of clockwise (CW) and counterclockwise (CCW) trapezoidal stimulation around the vertical axis with an acceleration of $20°/s^2$ up to a constant angular velocity of 60°/s. The axis of rotation is then tilted to an angle of 13° off vertical. The constant velocity rotation is maintained in this position for 2 minutes after which the axis of rotation is returned to a vertical position. Finally, the rotation is stopped with a deceleration of $20°/s^2$. Movements of both eyes are recorded by DC electronystagmography with horizontal and vertical leads. The OVAR elicited a unidirectional nystagmus beating toward the direction of the rotation (Fig 3). Based on the slow phase velocity (SPV) of the nystagmus,

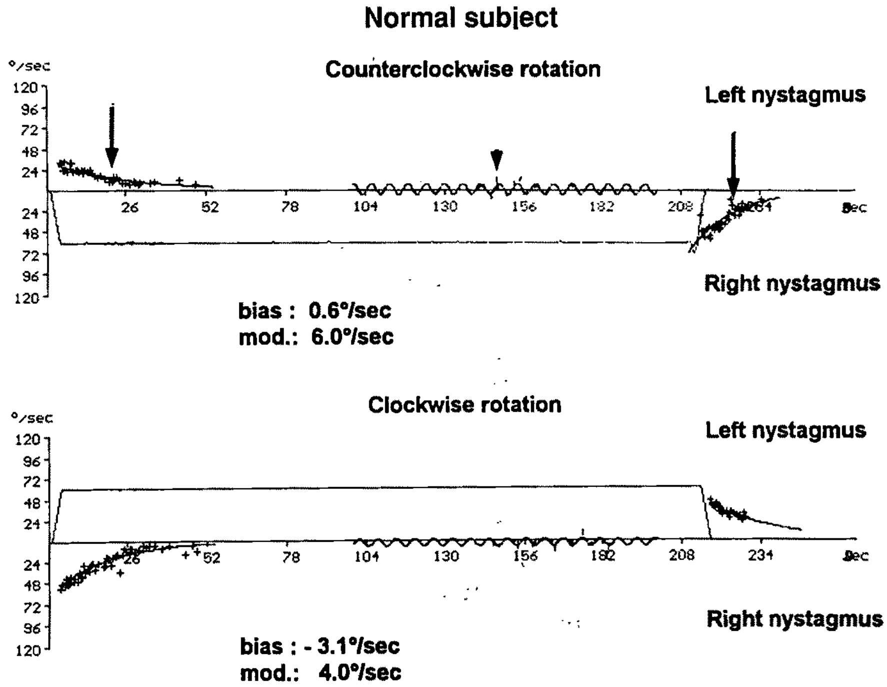


Fig 3. Slow phase velocity (SPV) of nystagmic responses recorded in normal subject undergoing off-vertical axis rotation (OVAR) testing. Canal response is elicited during phase of acceleration (left arrow). Axis of rotation is then tilted and frequency of rotation is kept constant for 2 minutes. Nystagmus beating in sense of rotation is detectable. Its periodic modulation (arrowhead) corresponds to fluctuation of SPV during OVAR and reflects otolithic organ response. Bias, negative during clockwise rotation and positive during counterclockwise rotation, is mathematical average SPV periodic fluctuation, and corresponds to nonzero baseline. Canal response reappears during phase of deceleration (right arrow).

the modulation and the bias are calculated by the same mathematical formula used by Furman et al.[9] The modulation corresponds to the periodic fluctuation of the SPV during the constant angular velocity rotation around the tilted axis and is thought to reflect an otolithic organ response.[8,9] The bias is the mathematical average SPV periodic fluctuation, which corresponds to a nonzero baseline. It is negative during CW rotation and positive during CCW rotation.

In the child with CHARGE association, the OVAR elicited a nystagmic response with an asymmetric horizontal modulation and negative bias in both CW and CCW rotations (Fig 4). The values of the modulation and bias compared to normative data obtained in the same laboratory in 15 healthy volunteers 24 to 50 years old are shown in the Table.

DISCUSSION

The incidence of CHARGE association has been estimated at 1 in 12,000 births.[14] The morbidity and prognosis depend on the severity of cardiac and/or

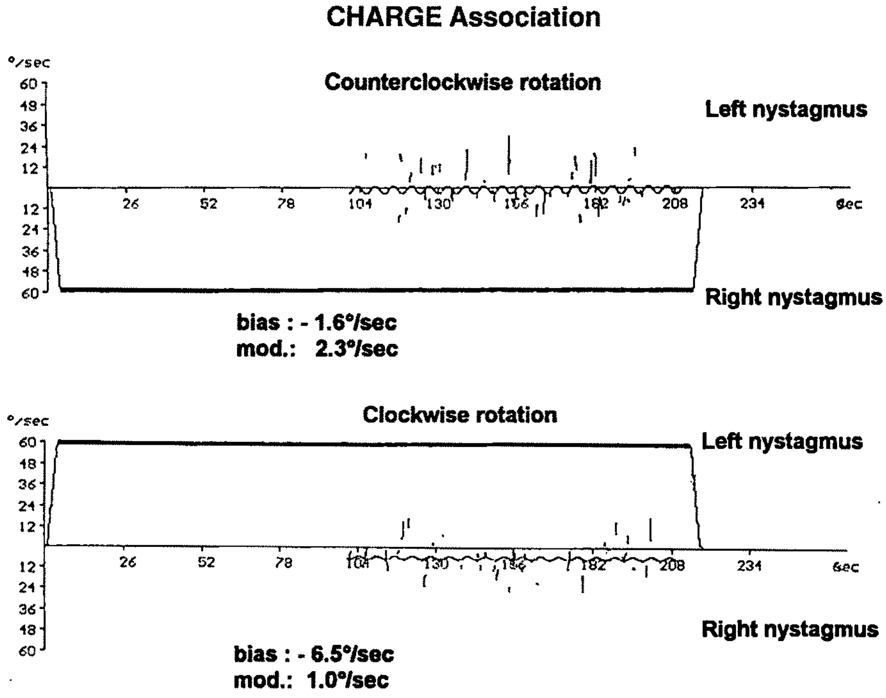


Fig 4. SPV of nystagmic response during OVAR testing in child with CHARGE association. There is no canal response during acceleration and deceleration. Nystagmic response is detected during constant-velocity rotation. Modulation of SPV of this response is lower than normal during clockwise and counterclockwise rotation; bias is negative during both counterclockwise and clockwise rotation.

MODULATION AND BIAS VALUES OF NYSTAGMUS ELICITED BY OFF-VERTICAL AXIS ROTATION

	Modulation (°/s)		*Bias (°/s)*	
	CW	*CCW*	*CW*	*CCW*
Normative values	7.7 ± 4.3	6.7 ± 2.8	−2.6 ± 4.3	1.2 ± 3.9
Case of CHARGE	1.0	2.3	−6.5	−1.6

Values measured in child with CHARGE association are significantly lower than normative values (mean ± SD), which were established in 15 normal subjects 24 to 50 years old (mean 30 years). Because utricle is missing in CHARGE dysplasia of temporal bone, this response is assumed to be saccular in origin.

CW — clockwise sense of rotation, CCW — counterclockwise sense of rotation.

CNS anomalies. In the absence of major heart and CNS defects, our patient developed almost normally. At the age of 8 years, he was able to undergo an extensive evaluation of vestibular function. Caloric and pendular rotatory stimulation did not elicit a nystagmic response, but a definite ocular response was elicited by OVAR. Although values for the modulation of the SPV of the nystagmus in CW and CCW rotations were lower than normal and values for the bias were negative during CW as well as CCW rotations, they indicate that an otolithic vestibular end organ was activated. Temporal bone CT demonstrated bilateral anomalies of the bony labyrinth typical of CHARGE dysplasia.[3] All 3 semicircular canals were absent, and there was a Mondini's dysplasia of the cochlea. On the basis of previous histologic descriptions of temporal bone CHARGE dysplasia,[2,3] it is assumed that the utricle was also absent but that the saccular macule was well formed. Therefore, it is logical to conclude that the response induced by the OVAR was saccular in origin.

Some investigators have suggested the possibility of gravity receptors in organs other than the inner ear that would be stimulated by the OVAR test.[15] If such somatosensory receptors exist, no convincing data show that their stimulation can elicit a direction-dependent nystagmic response. Instead, the fact that the nystagmic response to OVAR is not modified by a canal occlusion but is abolished after bilateral vestibular neurectomy strongly supports the concept that the response is otolithic in origin.[11,12] Today, no method exists to differentiate the saccular from the utricular components of the nystagmic response. Based on the planes of the utricular and saccular macules, it is reasonable to assume that the OVAR test is mainly a stimulus for the utricular macule, whereas off-horizontal axis rotation would be the primary stimulus for the saccular macule. Unfortunately, we were not able to perform an off-horizontal axis rotation test in our patient to compare the response to that obtained with the OVAR test.

The CHARGE dysplasia of the temporal bone is characterized by the presence of the saccule as the sole vestibular sense organ and by a malformed cochlea.[2,3] This particular dysplasia reaffirms the relationship of the saccule with the pars inferior of the labyrinth rather than with the pars superior[3] and may suggest that saccular function is nonvestibular on anatomic and phylogenetic grounds. However, the present observation of a nystagmic response elicited by the OVAR test supports anatomic[16] and physiological[17] studies that indicate that the saccule is a vestibular end organ. Since recent work has demonstrated that some saccular fibers send projections into the cochlear nucleus[18] and are acoustically responsive,[19] the mammalian saccule may have a dual function: auditory and vestibular.

The saccular response of a normal labyrinth may be different from that recorded in this model, given that the semicircular canals and utricle may interact with the saccule during normal activities,[12] and given the unknowns of the current anomalies in the present case study and the lack of precise knowledge of saccule physiology. Therefore, CHARGE dysplasia represents a potential model for the study of saccular function in humans, but findings should not be assumed to represent normal saccular function.

No animal experimental model exists to study the development of posturomotor control with congenital aplasia of the vestibular sense organs. Although the CHARGE model is not a perfect one because of multiple associated deficits, the association represents a unique opportunity to evaluate posturomotor development in the absence of the 3 semicircular canals and utricle. Our patient grew and progressed normally except for a delay in walking. He was able to walk freely by the age of 2 years. He wears hearing aids and glasses to correct the hearing and visual deficits. At age 10 years, his physical activities are normal, including riding a bicycle. Unlike patients who have lost vestibular function bilaterally,[20] he does not complain of oscillopsia, vertigo, or imbalance. This case demonstrates that relatively normal posturomotor development can be achieved without the vestibular end organs. Since this child also suffers from severe visual impairment, we postulate that the somatosensory afferents provide the major input necessary for posturomotor development.

The literature concerning the ear anomalies in CHARGE association is abundant, but is often confined to external and middle ear malformations. Some studies mention the cochlear defect and the resulting sensorineural hearing loss.[14] A few papers mention structural anomalies of the superior labyrinth,[21] but reports dealing with vestibular function are rarer.[22] Our case illustrates that a delay in walking in CHARGE association does not always indicate CNS anomalies, as suggested by the letter "R" of the acronym, but that it may be a result of the severe impairment of vestibular and visual functions. Therefore, the evaluation of patients suffering from CHARGE association should include vestibular function tests.

ACKNOWLEDGMENTS — The authors thank Professor R. R. Gacek for his many interesting suggestions, D. Werdenberg, MD, for referring the patient to us, and the patient and his mother for their kind collaboration.

REFERENCES

1. Pagon RA, Graham JM, Zonana J, Yong SL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 1981;99:223-7.

2. Wright CG, Brown OE, Meyerhoff WL, Rutledge JC. Auditory and temporal bone abnormalities in CHARGE association. Ann Otol Rhinol Laryngol 1986;95:480-6.

3. Guyot JP, Gacek RR, DiRaddo P. The temporal bone anomaly in CHARGE association. Arch Otolaryngol Head Neck Surg 1987;113:321-4.

4. Fraser JS. A case of congenital deafness, showing malformation of the bony and membranous labyrinths on both sides. J Laryngol Otol 1927;42:315-21.

5. Paparella MM, el-Fiky FM. Mondini's deafness. Arch Otolaryngol 1972;95:134-40.

6. Sekhar HK, Sachs M. Mondini defect in association with multiple congenital anomalies. Laryngoscope 1976;86:117-25.

7. Paparella MM. Mondini's deafness. A review of histopathology. Ann Otol Rhinol Laryngol [Suppl] 1980;89(suppl 67).

8. Guedry FE. Orientation of the rotation axis relative to gravity: its influence on nystagmus and the sensation of rotation. Acta Otolaryngol (Stockh) 1965;60:30-48.

9. Furman JMR, Schor RH, Schumann TL. Off-vertical axis rotation: a test of the otolith-ocular reflex. Ann Otol Rhinol Laryngol 1992;101:643-50.

10. Furman JMR, Schor RH, Kamerer DB. Off-vertical axis rotational responses in patients with unilateral peripheral vestibular lesions. Ann Otol Rhinol Laryngol 1993;102:137-43.

11. Correia MJ, Money KE. The effect of blockage of all six semicircular canal ducts on nystagmus produced by dynamic linear acceleration in the cat. Acta Otolaryngol (Stockh) 1970; 69:7-16.

12. Cohen B, Suzuki JI, Raphan T. Role of the otolith organs in generation of horizontal nystagmus: effects of selective labyrinthine lesions. Brain Res 1983;276:159-64.

13. Darlot C, Denise P, Droulez J, Cohen B, Berthoz A. Eye movements induced by off-vertical axis rotation (OVAR) at small angles of tilt in man. Exp Brain Res 1988;73:91-105.

14. Edwards BM, Van Riper LA, Kileny PR. Clinical manifestations of CHARGE association. Int J Pediatr Otorhinolaryngol 1995;33:23-42.

15. Mittelstaedt H. Evidence of somatic graviception from new and classical investigations. Acta Otolaryngol Suppl (Stockh) 1995(suppl 520):186-7.

16. Gacek RR. The course and central termination of first order neurons supplying vestibular end-organs in the cat. Acta Otolaryngol [Suppl] (Stockh) 1969(suppl 254).

17. Wilson VJ, Gacek RR, Uchino Y, Susswein AJ. Properties of central vestibular neurons fired by stimulation of the saccular nerve. Brain Res 1978;143:251-61.

18. Kevetter GA, Perachio AA. Projections from the sacculus to the cochlear nuclei in the Mongolian gerbil. Brain Behav Evol 1989;34:193-200.

19. McCue MP, Guinan JJ. Sound-evoked activity in primary afferent neurons of a mammalian vestibular system. Am J Otol 1997;18:355-60.

20. Vibert D, Liard P, Häusler R. Bilateral idiopathic loss of peripheral vestibular function with normal hearing. Acta Otolaryngol (Stockh) 1995;115:611-5.

21. Morgan D, Bailey M, Phelps P, Bellman S, Grace A, Wyse R. Ear-nose-throat abnormalities in the CHARGE association. Arch Otolaryngol Head Neck Surg 1993;119:49-54.

22. Murofushi T, Ouvrier RA, Parker GD, Graham RI, da Silva M, Halmagyi GM. Vestibular abnormalities in CHARGE association. Ann Otol Rhinol Laryngol 1997;106:129-34.

Ann Otol Rhinol Laryngol 108:1999

CARBON DIOXIDE LASER MICROSURGERY OF BENIGN VOCAL FOLD LESIONS: INDICATIONS, TECHNIQUES, AND RESULTS IN 251 PATIENTS

MARC REMACLE, MD, PHD

GEORGES LAWSON, MD JEAN-BAPTISTE WATELET, MD

YVOIR, BELGIUM

Two hundred fifty-one carbon dioxide laser–assisted cases of microphonosurgery are reported. Our series includes 167 women (66.5%) and 84 men (33.5%), with a mean age of 41 (±11) years. Single lesions represent 67.8% (n = 170) of the cases, with 20% (n = 50) being nodules, 18% (n = 44) Reinke's edema, 9% (n = 23) polyps, 8% (n = 19) sulci and related lesions, 6% (n = 16) mucosal cysts, 4% (n = 10) scars, 2% (n = 4) granulomas, and 2% (n = 4) vascular corditis. The cases with 2 or 3 lesions represented 32% (n = 81). Carbon dioxide laser–assisted microphonosurgery is efficient, provided the working parameters are strictly adhered to: micromanipulator micropoint providing a 250-µm laser beam for a 400-mm working distance; 0.1-second single pulses; and maximum power of 3 W with the superpulse wave. Glutaraldehyde–cross-linked collagen remains our filling material of choice in cases of vocal fold atrophy. Fibrin glue is useful for covering the resection area and for setting the microflaps. Microphonosurgery cannot be dissociated from speech therapy, the planning and duration of which, in relation to the procedure, depend on the nature of the initial lesion. Twenty to 30 sessions are usually adequate, but 6 months may be necessary in the case of sulcus vergetures. Our operating technique is derived from the microphonosurgery procedures with cold instruments. In addition to the classic advantage with regard to hemostasis, the carbon dioxide laser micropoint seems to make the dissection of microflaps easier.

KEY WORDS — benign lesions, carbon dioxide laser, microsurgery, phonosurgery, vocal fold.

INTRODUCTION

Since the pioneering work of Strong and Jako[1] in the early 1970s, the carbon dioxide (CO2) laser has become an indispensable instrument in microsurgery of the larynx.[2] The technical progress brought about, among others, by the microspot micromanipulator, has allowed its use in the treatment of benign lesions of the vocal fold[3] with less reservation than in the past.[4] However, cold instruments are still generally being used in microphonosurgery,[5,6] the principal reasons being the fear of excessive resection and of damaging Reinke's space and/or the vocal ligament.[4,7] Nevertheless, we systematically employ the CO2 laser in microphonosurgery, and we report our experience with the microspot micromanipulator.

MATERIALS AND METHODS

Between April 1989 and March 1995, a total of 251 patients — 167 women (66.5%) and 84 men (33.5%) — underwent CO2 laser microphonosurgery. The mean age (±SD) was 41 ± 14 years (range 10 to 77).

The distribution of the patients according to lesions and observed associated lesions is shown in Table 1. Single lesions were found in 67.8% of cases (170 cases), with 20% of patients having nodules (50 cases), 18% Reinke's edemas (44 cases), 9% polyps (23 cases), 8% sulcus or related lesions (19 cases), 6% mucosal cysts (16 cases), 4% scars (10 cases), 2% granulomas (4 cases), and 2% vascular corditis (4 cases). In 32% of cases (81 cases), 2 or 3 lesions were associated (Fig 1).

The assessment was based on the clinical examination carried out by the physician and the speech therapist during the same consultation. This included videostroboscopy and measuring the maximum phonation time (in seconds), the phonation quotient (in milliliters per second), and the maximum and conversational voice intensities (in decibels).

Spectral voice analysis was also carried out. The analysis is interpreted in the form of a histogram with intensity as the abscissa and frequency as the ordinate. The frequency scale was measured from 0 to 1,000 Hz or from 0 to 5,000 Hz, so as to determine the fundamental frequency (F0) and the first harmonics. Interpretation is qualitative, and voices are grouped into 5 classes according to criteria defined previously.[8]

Microphonosurgery is indissociable from speech therapy. The association between these two treatments varies according to the lesion. In the case of nodules, which are the consequence of vocal abuse,

---

From the Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital of Louvain at Mont-Godinne, Yvoir, Belgium.

CORRESPONDENCE — Marc Remacle, MD, PhD, Dept of Otorhinolaryngology–Head and Neck Surgery, University Hospital of Louvain at Mont-Godinne, B-5530 Yvoir, Belgium.

TABLE 1. BREAKDOWN OF CASES

	No.	*%*
Nodules	50	19.9
Reinke's edema	44	17.5
Polyp	20	8.0
Mucosal cyst	16	6.4
Reinke's edema with edematous polyp	9	3.6
Nodule with polyp	8	3.2
Bilateral sulci (furrows)	7	2.8
Bilateral scars	6	2.4
Nodules with bilateral sulci	6	2.4
Polyp with sulcus	6	2.4
Nodules with sulcus	5	2.0
Granuloma	4	1.6
Scar	4	1.6
Vascular corditis	4	1.6
Bilateral epidermoid cysts	3	1.2
Bilateral polyps	3	1.2
Nodule with mucosal cyst	3	1.2
Nodule with sulcus	3	1.2
Polyp with epidermoid cyst	3	1.2
Sulcus	3	1.2
Sulcus with epidermoid cyst	3	1.2
Bilateral sulci (furrows) with mucosal bridge	2	0.8
Nodule with sulcus and epidermoid cyst	2	0.8
Nodule with sulcus and mucosal bridge	2	0.8
Nodules with bilateral sulci (furrows) and mucosal bridge	2	0.8
Nodules with Reinke's edema	2	0.8
Nodules with sulcus and mucosal bridge	2	0.8
Reinke's edema with sulcus	2	0.8
Bilateral polyps with sulcus	1	0.4
Bilateral sulci (furrows) with mucosal bridge and scar	1	0.4
Bilateral sulci with bilateral scars and granuloma	1	0.4
Epidermoid cyst	1	0.4
Granuloma with anterior synechia	1	0.4
Mucosal cyst with microweb	1	0.4
Nodule with bilateral sulci	1	0.4
Nodule with polyp and epidermoid cyst	1	0.4
Nodule with scar	1	0.4
Nodules with bilateral sulci and microweb	1	0.4
Nodules with microweb	1	0.4
Polyp with bilateral sulci	1	0.4
Polyp with bilateral sulci (furrows)	1	0.4
Polyp with scar	1	0.4
Polyp with sulcus and epidermoid cyst	1	0.4
Polyp with sulcus and scar	1	0.4
Reinke's edema with bilateral epidermoid cysts	1	0.4
Reinke's edema with bilateral sulci	1	0.4
Reinke's edema with bilateral sulci and mucosal bridge	1	0.4
Reinke's edema with epidermoid cyst	1	0.4
Reinke's edema with mucosal cyst	1	0.4
Reinke's edema with edematous polyp and scar	1	0.4
Reinke's edema with edematous polyp and sulcus and epidermoid cyst	1	0.4
Sulcus with epidermoid cyst and microweb	1	0.4
Sulcus with mucosal cyst	1	0.4
Sulcus with scar	1	0.4
Teflon resection with collagen injection	1	0.4
Total	251	100

microsurgery is generally decided on after speech therapy, if the latter gives insufficient results.

Speech therapy is also undertaken as the first step in the case of a small lesion, such as a small sulcus vocalis, a scar, or a vascular corditis, where it may be quite sufficient on its own. On the other hand, when the lesions are more extensive and definitive and where speech therapy alone would be insufficient, the operation is undertaken straightaway, and is followed by speech therapy. This is the case with a polyp, Reinke's edema, cyst, or sulcus vergeture. Sulcus vocalis proper is an invagination of the covering epithelium that extends through the superficial lamina propria level to adhere to the vocal ligament. Sulcus vergeture is a term derived from the French word *vergeture* that may be used to describe atrophic changes in the skin, as in striae gravidarum (striae atrophicae). In the larynx, sulcus vergeture describes an atrophic depression along the free margin of the vocal fold. The medial margin of the fold is bowed. The mucosa lining the vergeture is thin and atrophic and tends to adhere to the underlying vocal ligament very closely.

The procedure is carried out under general anesthesia. If there are no contraindications from the anesthesiological point of view, we prefer to employ high-frequency jet ventilation[9] with the help of a metal catheter, for adults and children alike, that can be attached to all models of laryngoscope (Mayné-Remacle catheter). If, however, there are contraindications, then we use a flexible metal tube adapted for laser surgery (Mallinckrodt Medical, Athlone, Ireland).

The diameter of the CO_2 laser beam focalized by the microspot micromanipulator (Acuspot, Laser Industries, Tel Aviv, Israel) is 250 μm for a working distance of 350 mm. For this reason, the energy delivered is concentrated on a very much smaller area and therefore allows us to use less-powerful pulses to produce the same effect; the thermal diffusion around the target is thus reduced and the macroscopic cutting effect is improved, although, of course, the microscopic effect is still cellular vaporization. This improvement of the cutting effect, combined with that obtained by using the superpulse wave, allows us to section and dissect the epithelium off the vocal fold, which, although possible, was very painstaking to achieve with the older types of micromanipulators, which give beams with a diameter of 700 μm (or more) for a working distance of 400 mm.

The working parameters are beams with a diameter of power of 2 to 3 W and a single pulse of a 0.1-second, focused beam. In contrast, it is 1 W with

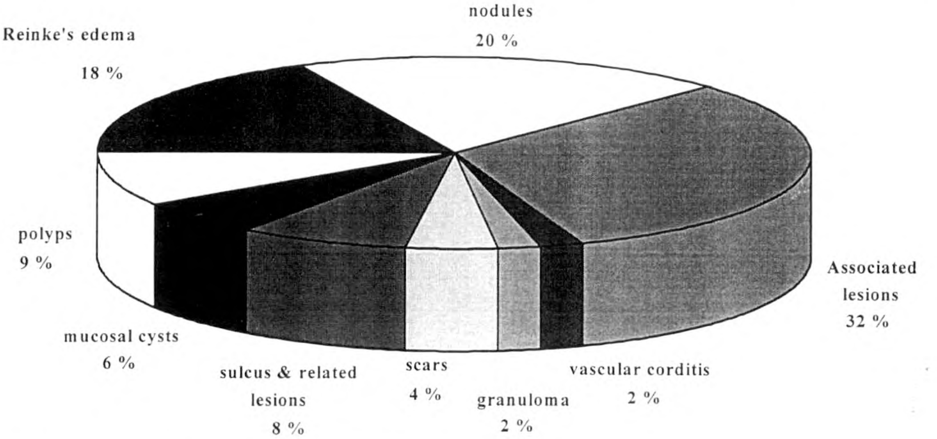


Fig 1. Breakdown according to lesions.

0.05-second pulses and a slightly defocused beam that is required to coagulate microvessels, as, for example, in the case of vascular corditis, or before sectioning the epithelium, in the case of Reinke's edema.

The procedure begins by a careful examination of the vocal folds to look for any associated lesion undetected during the preoperative assessment. As with the procedure with cold instruments, the lesion or the free edge of the vocal fold is pulled toward the midline with microforceps (Bouchayer, Micro-France, Paris, France). Using the single-pulse mode is necessary to control the cutting or the resection while avoiding the risk of damaging the vocal ligament. Small cotton swabs, soaked in saline containing epinephrine and cooled to 5°C, are used to control any slight superficial bleeding. Nodules, polyps, and small sulci, called open cysts by Bouchayer and Cornut,[5] as well as mucosal bridges, mucosal and epidermoid cysts, and granulomas, are the lesions that are resected, whereas Reinke's edemas, large sulci, and scars, on the other hand, undergo dissection.

The lesions to be resected are gripped with the microforceps and pulled toward the midline of the larynx, well away from the vocal ligament. The sectioning is carried out in Reinke's space and as close as possible to the lesion (Fig 2).

In the case of Reinke's edema, the procedure is derived from that of Gould and Hirano (see Hirano[10]). The operation begins by coagulating the microvessels on the upper surface of the vocal fold. Then, the epithelium is incised along the length of the upper surface, from the vocal process up to 2 to 3 mm from the anterior commissure. After the incision, the freed flap is pulled away toward the midline with Bouchayer forceps, and the accumulated fluid within Reinke's space is aspirated. The microflap, held by the forceps, is then put back in place. If the Reinke's edema is more voluminous, then any excess epithelium is resected so as to get a better edge-to-edge fit of the incision. The two vocal folds are operated on at the same time, provided 2 to 3 mm of mucosa near the anterior commissure is untouched.

In the case of sulci and scars, the procedure is based on that of Bouchayer et al.[11] The incision starts

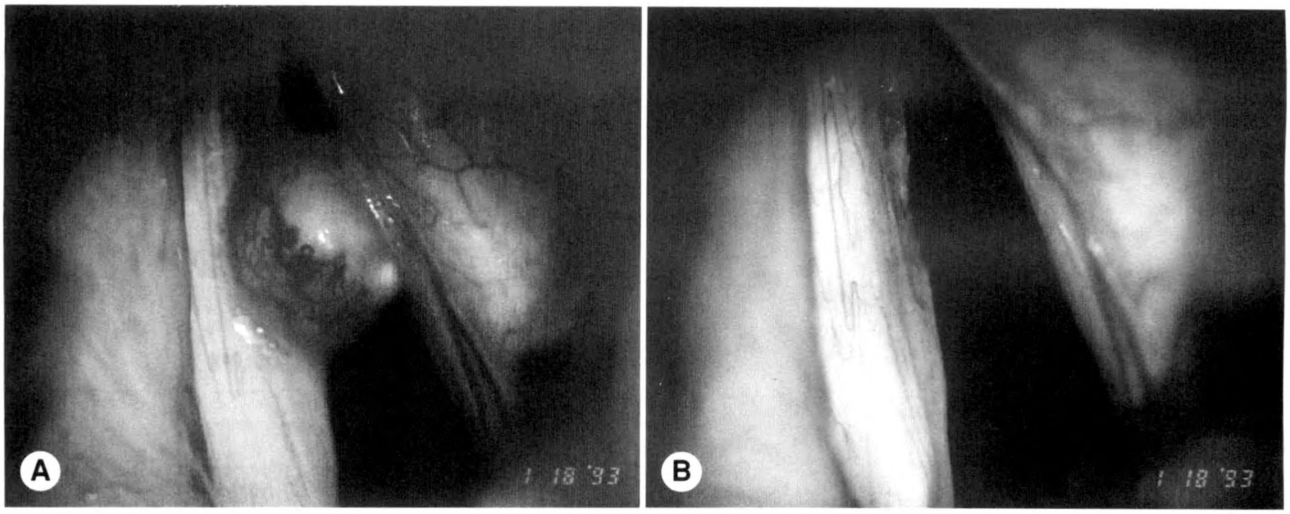


Fig 2. Patient with angiectatic polyp. A) Before resection. B) After resection.

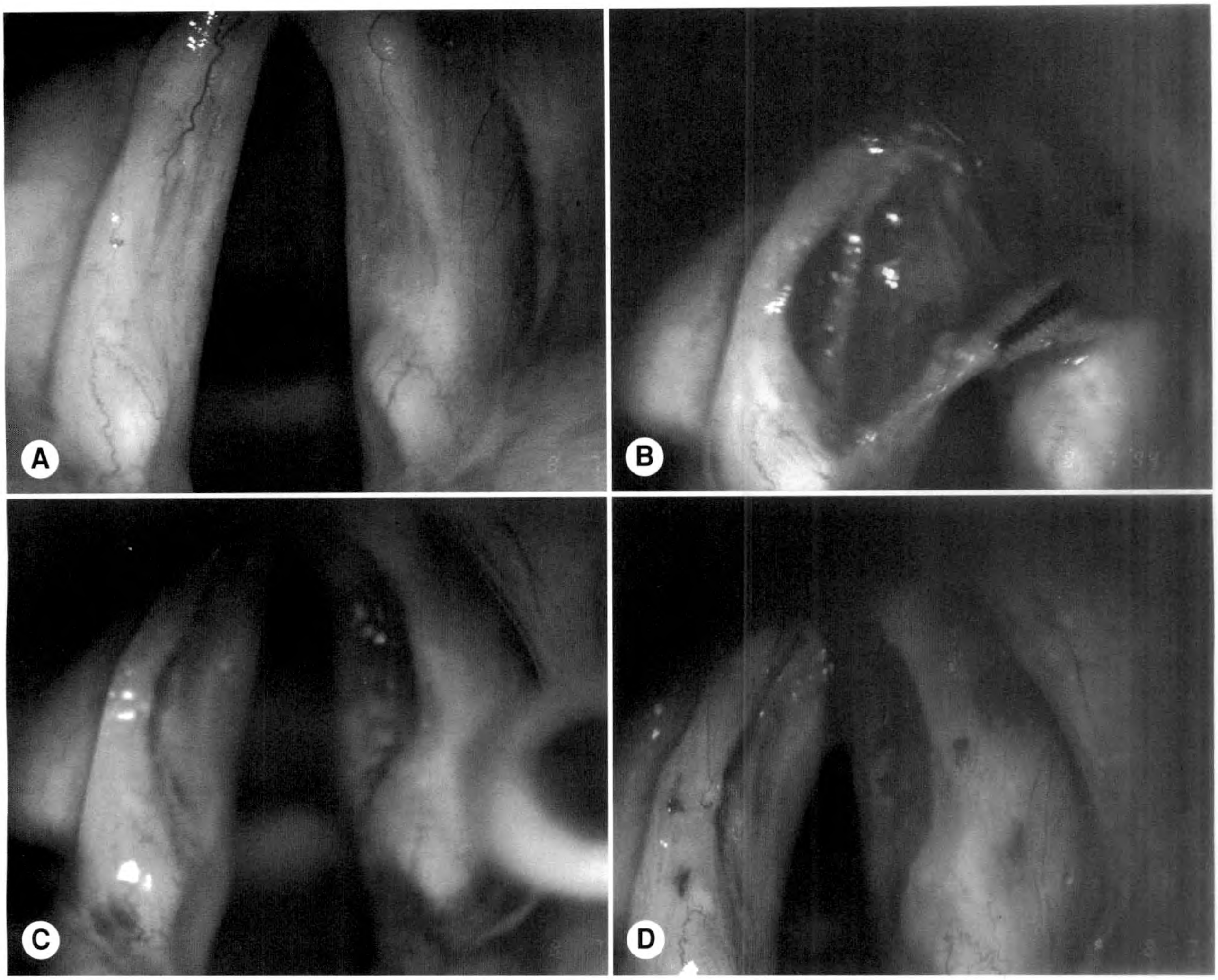


Fig 3. Case of bilateral sulcus vergeture. A) Exploration. B) Dissection of epithelium. C) Glutaraldehyde–cross-linked collagen injection to correct vocal fold atrophy. Right vocal fold is being injected. Tip of injection device is visible. D) Microflaps are redraped after applying some drops of fibrin glue.

on the external upper edge of the lesion. The epithelium is then seized with the Bouchayer forceps on the internal side of the incision, and the dissection is continued carefully by following the epithelium as closely as possible. During the dissection, it is important to take all the dissected epithelium so as to separate it as much as possible from the vocal ligament up to the lower surface of the vocal fold (Fig 3A,B). In the event of sulcus vergeture, sulcus corresponding to actual vocal fold atrophy, or a scar resulting in a significant defect, we finish the procedure by an injection of glutaraldehyde–cross-linked (GAX) collagen (Zyplast, Collagen Corporation, Palo Alto, Calif)[12] in order to obtain a vocal fold volume as near to normal as possible (Fig 3C).

The injection is carried out, whenever possible, into the lamina propria. It is, nevertheless, more difficult than injections for paralysis,[13] where Reinke's space is intact. It is the preliminary dissection that ensures the correct injection of the collagen, which would otherwise diffuse around the zone needing enlargement without actually filling it. It is important to obtain symmetric vocal fold volume, and the injection is made in one or the other of the vocal folds, depending on whether the volume insufficiency is unilateral or bilateral.

The amount injected varies from 0.2 to 0.6 mL per vocal fold. In the case of a unilateral injection, this is judged to be sufficient when a volume similar to that of the contralateral fold is obtained. In the case of bilateral injection, it is judged to be sufficient when the free edge of the vibrating part of the vocal folds reaches the midline.

At the end of the procedure, we apply several drops of fibrin glue (Tissucol, Immuno, Vienna, Austria) in slow-setting mode, either to cover the resected zone or to redrape the microflap (Fig 3D).

The specimen removed during the operation is routinely sent for histologic examination. This examina-

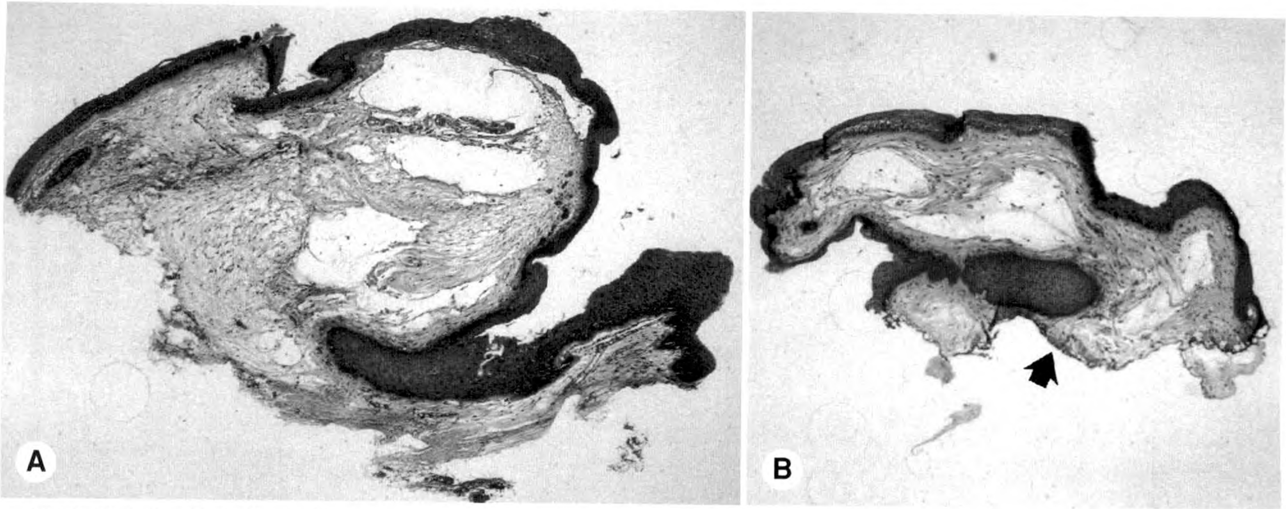


Fig 4. Nodules (H & E). A) Nodule resected with microscissors. B) Nodule resected with carbon dioxide laser. Parameters: micropoint micromanipulator; single-pulse mode; 0.1-second duration per pulse; 3-W power; superpulse wave; 400-mm working distance. Coagulation of margin is only several microns thick (arrow).

tion is always possible, even in the case of a nodule, because the edge of the section where the cut was made is only a few microns thick (Fig 4).

After the operation, the patient is taken back to his or her room and can be discharged the evening of the same day, provided there is someone to take the patient home.

Strict vocal rest for 8 days is recommended. The medical treatment is based essentially on aerosol steroids and oral antibiotics for 8 to 10 days. The first control is carried out 8 to 10 days after the procedure, and phonation is resumed under the supervision of a speech therapist.

RESULTS

A predominance of women is found in these groups of patients ($p < 10^{-5}$; nodules 84%; Reinke's edema 64%; other lesions 65%), except in the group with polyps, which has a majority of men (71%).

The youngest population is the group with nodules, whose median age of 33 years is significantly lower than the ages of the groups with polyps ($p = .001$), with Reinke's edema ($p < 10^{-5}$), or with sulci, scars, or mucosal cysts ($p = .003$). The age of the group with Reinke's edema (median 49 years) is also significantly higher than the ages of the groups with nodules, with polyps ($p = .001$), or with other lesions ($p = .020$).

The distribution of the lesions was such that 32% of cases had 2 or 3 associated lesions (Table 1; Fig 1). Among these associated lesions, 19 (23%) were identified with certainty during the preoperative assessment, 42 (52%) were suspected and later confirmed during the perioperative examination, and 20 (25%) were only identified during the perioperative examination. It was especially the small sulci and associated lesions (microwebs, mucosal bridges), epidermoid cysts, and small scars that were identified with certainty during perioperative exploration.

For analyzing the results, the patients were classified into 7 groups according to 1 lesion, either alone or associated, so as to make a better judgment of the relative significance of this lesion in comparison to the entire series. There were 7 groups of lesions: nodules, 88 cases (30%); Reinke's edema, 63 cases (22%); polyps, 57 cases (20%); sulci and epidermoid cysts, 29 cases (10%); mucosal cysts, 21 cases (7%); scars, 19 cases (7%); and miscellaneous, 11 cases (4%). The last group consisted of 5 cases of granuloma, 5 cases of vascular corditis, and 1 case of Teflon resection with injection of GAX collagen.

In the nodule group, the median value of the spectral voice analysis revealed an improvement from class 3 to class 4. The median F_0 increased from 200 to 210 Hz. The median maximum phonation time improved from 13 to 17 seconds, and the median phonation quotient fell from 245 to 200 mL/s. Median conversational intensity, at 62 dB, remained stable, as did the median maximum voice intensity, ranging from 89 to 94 dB.

In the Reinke's edema group, the median value of the spectral voice analysis did not change after the operation and remained at class 3, but the median F_0 increased from 160 to 182.5 Hz for this group of patients. The value of the median F_0 for the women alone showed an improvement from 170 to 195 Hz. The median maximum phonation time remained stable, with a median preoperative value of 15 seconds and a postoperative value of 17 seconds. The median

TABLE 2. BREAKDOWN ACCORDING TO ONE LESION, ALONE OR ASSOCIATED

	Patients		*Men*	*Women*	*Mean Age*
	No.	*%*	*(%)*	*(%)*	*± SD (y)*
Nodules	88	30	16	84	33 ± 11
Reinke's edema	63	22	36	64	49 ± 12
Polyps	57	20	71	29	41 ± 11
Sulci and epidermoid cysts	29	10	26	74	36 ± 11
Mucosal cysts	21	7	54	48	49 ± 19
Scars	19	7	16	84	42 ± 11
Miscellaneous	11	4			

phonation quotient fell from 250 to 164 mL/s, while the median conversational intensity (59 to 63 dB) was maintained, as was the maximal intensity (85 to 94 dB).

In the polyp group, the median value of the spectral voice analysis remained stable at class 3. The median F0 changed from 125 to 145 Hz, and the maximum phonation time improved from 15 to 17 seconds. The phonation quotient was improved from 265 to 205 mL/s. The median conversational intensity remained practically the same (60 to 62 dB), as did the maximal intensity (90 to 86 dB).

In the group with mucosal cysts, the median spectral voice analysis remained the same before and after the operation, at class 3. The median F0 improved from 189 to 220 Hz. The median maximum phonation time and the median phonation quotient improved from 13 to 16 seconds and from 212 to 173 mL/s, respectively. The median conversational intensity remained stable (67 to 63 dB), as did the maximal intensity (91 to 98 dB).

In the sulcus group, the median spectral voice analysis improved by passing from class 2 to class 3. The median F0 rose from 210 to 235 Hz. The maximum phonation time went from 12 to 14 seconds, and the phonation quotient improved from 375 to 291 mL/s. The median conversational intensity remained stable (61 to 63 dB), whereas the maximal intensity rose, from 73 to 93 dB.

In the group with scars, the median spectral voice analysis improved from class 2 to class 3. The median F0 rose from 205 to 220 Hz. The median maximum phonation time went from 15 to 16.5 seconds, and the phonation quotient was brought down from 352 to 200 mL/s. The median conversational intensity increased from 54 to 59 dB, while the median maximal intensity rose from 72 to 89.5 dB. These data are summarized in Tables 2 and 3.

The first control generally took place between the 8th and 10th days. In the case of small lesions, stroboscopy showed a satisfactory recovery of vibratory amplitude, as well as the return of a mucosal wave motion on the upper surface of the vocal fold. In the case of nodules, the vibration is usually symmetric, whereas it may remain slightly asymmetric in cases of polyps, mucosal cysts, epidermoid cysts, or small sulci, but without affecting the voice or giving rise to diplophonia.

The recovery of vibration, as observed by stroboscopy, takes longer in Reinke's edema, given the extent of the dissection, and is especially long in the case of a large sulcus or sulcus vergeture. A satisfactory recovery of vibration may take 3 to 4 weeks in the case of Reinke's edema, but it may be as long as 3 to 4 months in the case of sulcus vergeture. In these cases of vergetures, although the vibration improved, it did not become normal. The closure of the glottis was improved, but was still often incomplete; and the vibration frequently remained asym-

TABLE 3. MEDIAN VOICE RESULTS

	Spectral Voice Analysis (grade)		*F0 (Hz)*		*MPT (s)*		*PQ (mL/s)*		*Conv Int (dB)*		*Max Int (dB)*	
	Preop	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
Nodules	3	4	200	210	13	17	245	200	62	62	89	94
Reinke's edema	3	3	160	182.5	15	17	250	164	59	63	85	94
			170*	195*								
Polyps	3	3	125	145	15	17	265	205	60	62	90	86
Mucosal cysts	3	3	189	220	13	16	212	173	67	63	91	98
Sulci and related lesions	2	3	210	235	12	14	375	291	61	63	73	93
Scars	2	3	205	220	15	16.5	352	200	54	59	72	89.5

F0 — fundamental frequency, MPT — maximum phonation time, PQ — phonation quotient, Conv Int — conversational intensity, Max Int — maximum intensity.

*Female patients only.

metric in phase, even if the amplitude became normal. A wave motion was sometimes seen to return.

Immediate complications were rare. We deplored 1 case of loosened teeth in a patient with periodontitis and a small mouth opening, and 2 cases of luxation of dental posts due to retrognathia.

The follow-up of the patient was usually continued until the voice quality for his or her needs was reached and when an objective result, depending on the initial lesion, was obtained. The median follow-up is 3 months for Reinke's edema, polyp, or mucosal cyst. It is 4 months for small sulcus, 5 months for scars and sulcus vergetures, and 6 months for nodules (preoperative speech therapy included).

Subjectively, the patients themselves observed that the voice had returned to normal in the cases of nodules, polyps, and mucosal cysts. This was also the case with small sulci. In Reinke's edema, the pitch was improved, especially in women.

The result was maintained in the case of nodules, inasmuch as the hyperkinetic dysphonia at the origin of nodules was itself well corrected by speech therapy. Similarly, in Reinke's edema, abstention from tobacco guarantees that voice quality is maintained.

In cases of scars or sulcus vergetures, the patients observed a better capacity for vocal effort with a reduction in fatigue and a better tone. Breath, hoarseness, and voice instability were improved. Nevertheless, one cannot really claim that there was an integral recovery in the case of a scar, or that a normal voice was obtained in cases of sulcus vergetures.

DISCUSSION

The classic notions are confirmed, with regard to the population under study.[14] Indeed, the majority of the population were professionally active adults, for whom the voice is a professional tool for communicating.

Whereas a nodule is essentially the consequence of hyperfunctional dysphonia and vocal abuse,[14] a polyp is the result of multiple factors (tobacco, respiratory irritants, allergy), but above all, seems to be particularly influenced by intense, violent vocal efforts with brutal variations in subglottic pressure,[15] found in voices used to command, which might explain the predominance of men in this group.[16]

The higher age in the group with Reinke's edema can be explained by the time required for the lesions caused by tobacco abuse to arise. The predominance of women in this group is probably due to the deterioration of the voice, more embarrassing for women than for men, which encourages them to seek medical treatment more willingly.

The frequency of cases with 2 or 3 associated lesions has led us to prefer direct laryngoscopic procedures under general anesthesia, rather than indirect laryngoscopic techniques with local anesthesia.[17] Of course, the preoperative assessment, based on videostroboscopy, allows us to detect vibration disorders and to suspect lesions that cannot be seen by the naked eye, but like Bouchayer and Cornut,[5] we believe that a large number of lesions can be detected or confirmed during exploration with a microscope, with palpation and unfolding of the vocal fold. These lesions are overlooked when the diagnosis is determined with indirect laryngoscopy, even with stroboscopy. Further, although it is possible and even easy to remove lesions on the free edge of the vocal fold, such as nodules or polyps, with these indirect procedures, delicate intracordal dissection of a cyst or sulcus is impossible.

The ventilation mode used during general anesthesia is left to personal choice and depends on the preference and experience of the anesthetist. It is important that the patient is well relaxed, and not in a condition to produce sudden, untimely movements of the vocal fold during the operation, and that the exposure is such that the vocal fold can be reached throughout its entire length. As far as we are concerned, we prefer high-frequency ventilation whenever possible, which ensures the largest operating field. It is true, however, that the subglottic region is not protected from a shot of the laser beam with this technique. These impacts usually hit the anterior part of the cricoid cartilage or the first tracheal ring. However, due to the working parameters used, and the defocalization of the beam beyond the target, the impacts are harmless, and have never given rise to any complications in our series of patients; at the most, they produced a slight surface coagulation.

The choice of the instrument also depends on the phonosurgeon's experience and training. As far as we are concerned, given the availability of micropoint micromanipulators, we prefer to use a laser, contrary to general opinion.[18]

Provided the working parameters are strictly respected, one can take advantage of the CO_2 laser without fear of the problems that arise with the older types of micromanipulator.[7] The coagulation of only a few microns (Fig 4) eliminates or reduces perioperative bleeding and makes sectioning or dissecting easier. The absence of carbonization allows one to follow closely the progression of the dissection of Reinke's space, and thus avoids any damage to the vocal ligament. The precision of the cut is guaranteed by working in the single pulse mode. Working in the

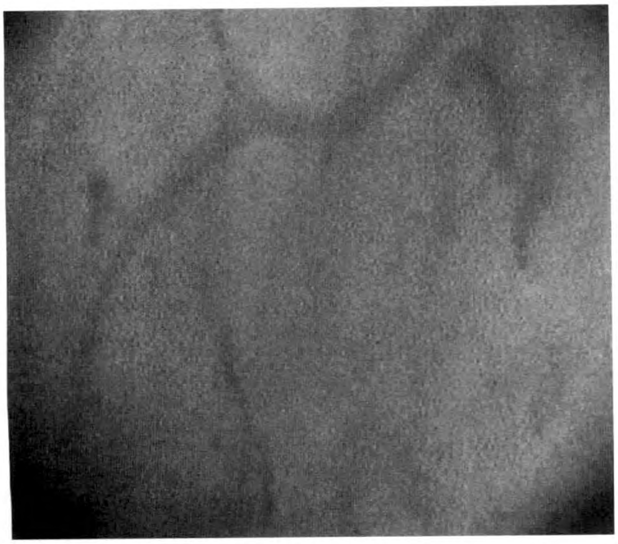


Fig 5. Persistence of vascular flow within microvessels in Reinke's space after resection of nodule (original ×150). (Contact endoscopy according to Andrea et al[19]; contact endoscope from Wolf, Tuttlingen, Germany.)

continuous mode is prohibited.

We have observed (Fig 5), by using the contact endoscopy technique of Andrea et al,[19] the flow of red blood cells in the microvessels of Reinke's space after section or dissection with the CO2 micropoint laser, demonstrating the absence of any in-depth thermal damaging effects.

In our experience, the CO2 micropoint laser makes microsurgery easier for the treatment of angiectatic polyps, Reinke's edema, sulci, sulcus vergetures, granulomas, and scars. It is equivalent to cold instruments for treating nodules, edematous polyps, and mucosal and epidermoid cysts.

Apart from the choice of instrument, our operating technique and indications are those of Bouchayer and Cornut.[5] Thus, at the end of surgery, we cover the resected zones and redrape the microflaps with fibrin glue. Its use is empirical, but it seems to enhance healing, it makes the redraping of microflaps easier, and it reduces the risk of granuloma formation.

In the case of vocal fold atrophy, whether acquired or congenital, it is advisable to increase the volume of the vocal fold by injection of GAX collagen.[20,21] Dissecting the zone of fibrosis is indispensable; otherwise, the collagen would diffuse around the zone to be filled without really increasing its volume. In our opinion, GAX collagen is the least unfavorable material for correcting glottic insufficiency by endoscopic means.[22] The desired amount can be injected into Reinke's space with a small-diameter needle (27-gauge), as cannot be done with fat or Teflon. Moreover, GAX collagen does not induce the inflammatory reactions seen with Teflon. The stability of the results from the functional point of view is 4.5 years (median) for the correction of glottic insufficiency caused by vocal fold immobility. It has, further, the advantage over autologous collagen[23] of being available immediately if necessary during the operation. It also seems to us to be more adapted than type I thyroplasty, as described by Isshiki et al,[24] for the filling of glottic gaps caused by atrophy, which are usually less significant than those resulting from paralysis.

Speech therapy is indispensable following microphonosurgery. Its duration is variable, depending on the indication and the time required for the patient to integrate correct vocalization. The longest duration is encountered in cases of sulcus vergetures (up to 6 months). The reason is that it is necessary to suppress the hyperfunctional compensation that the patient had adopted before the operation, sometimes many years earlier. Further, the procedure itself induces fibrosis, even though the purpose of the procedure is to correct as much as possible the preoperative fibrosis and the glottic gap (which were far worse).

In the case of sulcus vergetures, as well as scars, the patient cannot be promised a complete recovery of the vocal fold.[5] On the other hand, the dysesthesia and vocal fold fatigue are greatly reduced, and the tone will be improved as a result of a better vibration of the vocal fold. The vocal comfort of the patient will be globally increased. It is therefore necessary to explain the limitations of the operation and to be assured of the patient's determination and cooperation in long-term treatment.

The voice measurements we have used depended on the instruments available at the time of operation. Apart from software used to analyze the voice spectrum, the tests are simple and easily carried out in everyday practice. Undoubtedly, new software, giving rise to an objective multiparametric study,[25] will allow us to refine the measurements.

CONCLUSIONS

The progress made in CO2 laser technology has allowed use of laser-assisted microphonosurgery, provided the working parameters are strictly respected. The frequency of associated lesions identified by a careful examination under direct laryngoscopy is an argument against indirect laryngoscopic procedures under local anesthesia.

The preoperative assessment, the postoperative follow-up, and speech therapy are all mandatory for successful treatment. It is important to explain to the patient what outcome may be expected according to the initial lesion. Thus, whereas one can commit one-self to a return to a normal voice in the case of nodules or polyps, the microsurgery of congenital or acquired vocal fold atrophies, such as sulcus vergetures or scars, cannot give rise to such high expectations.

REFERENCES

1. Strong MS, Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO2 laser. Ann Otol Rhinol Laryngol 1972;81:791-8.

2. Duncavage JA, Aly A, Halter S, Ossoff RH. Laser surgery in the larynx. In: Ford CN, Bless DM, eds. Phonosurgery. Assessment and surgical management of voice disorders. New York, NY: Raven Press, 1991:167-81.

3. Shapshay SM, Rebeiz EE, Bohigian RK, Hybels RL. Benign lesions of the larynx: should the laser be used? Laryngoscope 1990;100:953-7.

4. Vaughan CW, Blaugrund SM, Gould WJ, Hirano M, Ossoff R, Sataloff RT. Discussion: surgical management of voice disorders. J Voice 1988;2:176-81.

5. Bouchayer M, Cornut G. Microsurgical treatment of benign vocal fold lesions: indications, technique, results. Folia Phoniatr (Basel) 1992;44:155-84.

6. Courey MS, Gardner GM, Stone RE, Ossoff RH. Endoscopic vocal fold microflap: a three-year experience. Ann Otol Rhinol Laryngol 1995;104:267-73.

7. Tanaka S, Hirano M, Chijiwa K. Some aspects of vocal fold bowing. Ann Otol Rhinol Laryngol 1994;103:357-62.

8. Remacle M, Trigaux I. Characteristics of nodules through the high-resolution frequency analyser. Folia Phoniatr (Basel) 1991;43:53-9.

9. Mayné A, Collard E, Delire V, Randour P, Joucken K, Remacle M. Laryngeal laser microsurgery: airway and anesthetic management. Hospimedica 1991;9:32-6.

10. Hirano M. Endolaryngeal microsurgery. In: English GM, ed. Otolaryngology. Vol 3. Philadelphia, Pa: Lippincott, 1988:1-11.

11. Bouchayer M, Cornut G, Loire R, Roch JB, Witzig E, Bastian RW. Epidermoid cysts, sulci and mucosal bridges of the true vocal cord; a report of 157 cases. Laryngoscope 1985; 95:1087-94.

12. Remacle M, Declaye X, Hamoir M, van den Eeckhaut J. CO2-laser treatment of the sulcus and of the epidermoid cyst. Technic and results. Acta Otorhinolaryngol Belg 1989;43:343-50.

13. Remacle M, Marbaix E, Hamoir M, Bertrand B, van den Eeckhaut J. Correction of glottic insufficiency by collagen injection. Ann Otol Rhinol Laryngol 1990;99:438-44.

14. Gould WJ, Rubin JS, Yanagisawa E. Benign vocal fold pathology through the eyes of the laryngologist. In: Rubin JS, Sataloff RT, Korovin GS, Gould WJ, eds. Diagnosis and treatment of voice disorders. New York, NY: Igaku-Shoin Publishers, 1995:137-51.

15. Roch JB, Cornut G, Bouchayer M. Mode d'apparition des polypes des cordes vocales. Rev Laryngol Otol Rhinol (Bord) 1989;110:389-90.

16. Kleinsasser O. Pathogenesis of vocal cord polyps. Ann Otol Rhinol Laryngol 1982;91:378-81.

17. Milutinovic Z. Indirect microsurgery of the vocal folds. Videostroboscopy vs. microstroboscopy. Ear Nose Throat J 1993;72:134-6, 141.

18. Werkhaven J, Ossoff RH. Surgery for benign lesions of the glottis. Otolaryngol Clin North Am 1991;24:1179-99.

19. Andrea M, Dias O, Santos A. Contact endoscopy of the vocal fold. Normal and pathological patterns. Acta Otolaryngol (Stockh) 1995;115:314-6.

20. Remacle M, Lawson G, Sasserath M, Claremunt R. Treatment of sulcus glottidis by association of CO2-laser and collagen. J Fr Otorhinolaryngol 1993;42:29-32.

21. Ford CN, Bless DM. Collagen injection in the scarred vocal fold. J Voice 1987;1:116-8.

22. Remacle M, Dujardin J-M, Lawson G. Treatment of vocal fold immobility by glutaraldehyde–cross-linked collagen injection: long-term results. Ann Otol Rhinol Laryngol 1995;104: 437-41.

23. Ford CN, Staskowski PA, Bless DM. Autologous collagen vocal fold injection: a preliminary study. Laryngoscope 1995;105:944-8.

24. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol (Stockh) 1975;80:465-73.

25. Giovanni A, Estublier N, Robert D, Teston B, Zanaret M, Cannoni M. Objective vocal evaluation of dysphonia by simultaneous measurement of acoustic and aerodynamic parameters with the EVA device. Ann Otolaryngol Chir Cervicofac 1995;112:85-90.

Ann Otol Rhinol Laryngol 108:1999

TELESCOPIC VIDEO MICROLARYNGEAL SURGERY

ALBERT REMING YEH, MD
HUNG-MENG HUANG, MD YU-LIN CHEN, MD
TAIPEI, TAIWAN

Although traditional microscopic laryngeal surgery has been well developed, we still may encounter some clinical problems, including exposure difficulty, blind areas during examination, and inadvertent cutting through lesions. These problems may lead to an increased risk of complications or protracted or even repeated operations. We have partially overcome these problems since October 1992 with a new telescopic endolaryngeal surgery technique. This technique was developed by combining and modifying the principles of bronchoscopic surgery and endoscopic sinus surgery. With this technique, it is not necessary to use a very slim laryngoscope or apply overpressure on the larynx when introducing and suspending the laryngoscope. Difficult-to-examine regions can be accessed more easily. We can also get a 3-dimensional impression of lesions and related structures, so it is easier to determine a proper cutting line to avoid cutting through lesions. We consider this telescopic method to be a useful alternative to conventional microscopic laryngeal surgery.

KEY WORDS — en bloc excision, exposure difficulty, telescopic laryngeal surgery, video microlaryngeal surgery, vocal cord.

INTRODUCTION

Traditional microscopic laryngeal surgery has developed since the 1960s. Generally speaking, phonosurgical principles and technique are well established and have rather good results. The technique was also applied to operations for early laryngeal carcinoma and respiratory papillomatosis in recent years.

However, with traditional laryngeal microsurgery, one encounters some problems during clinical practice. These include exposure difficulty,[1-3] a blind area in examination,[2-5] and the possibility of cutting through lesions. These problems can lead to increased risk of complications or reoperation.[1,6] We developed a telescopic endolaryngeal surgery technique 4 years ago in an attempt to overcome these problems.

MATERIALS AND METHODS

From October 1992 to August 1996, 14 problem patients received telescopic laryngeal surgery. Of these, 7 were males and 7 were females. Their ages ranged from 3 days old to 62 years old. Since some clinical problem arose for each patient during conventional microscopic laryngeal surgery — either a short, muscular neck, anatomic changes due to a huge laryngeal tumor, or cardiac arrhythmia caused by the force needed for suspension of the laryngoscope — we used this telescopic surgical technique to continue the operations (see Table).

This telescopic laryngeal surgery technique was developed by combining and modifying the principles of bronchoscopic surgery and endoscopic sinus surgery.[7] Zero-degree, 30°, and 70° Storz or Olympus telescopes are used to view the larynx and the lesion from above and behind. Both the 2.7-mm (or 2.5-mm) and 4.0-mm telescopes used in bronchoscopy or cystoscopy can be used. We can look through the telescope directly or via the monitor. The charge-coupled device cameras used include Aztec VCI-101 and Olympus OTV-F3 with universal adapters. Some modifications were made to the surgical instruments used in microscopic laryngeal and bronchoscopic surgery. The most important is a half cutting–half grasping microforceps (Fig 1).

During the operation, after standard intubation anesthesia is given, the laryngoscope is introduced gently, without overpressure on the larynx. The lesion and the larynx are examined from several directions with the angled telescopes. The sites are examined as completely as possible, including the anterior commissure, ventricles of Morgagni (Fig 2A), and undersurface of the vocal cords (Fig 2B). The incision line is determined according to the 3-dimensional (3-D) view of the lesion.

Since this is basically a 1-handed technique, the

From the Section of Otolaryngology, Taipei Municipal Women and Children Hospital (all authors), the Department of Otolaryngology, Chang Gung Memorial Hospital (Yeh), and the Department of Otolaryngology, College of Medicine, National Taiwan University (Huang), Taipei, Taiwan.

Abstract presented at the meeting of the Taiwan Otolaryngological Society, Taipei, Taiwan, November 9-10, 1995.

CORRESPONDENCE — Albert ReMing Yeh, MD, Dept of ENT, Taipei Municipal Women and Children Hospital and Lin-Kou Medical Center, Chang Gung Memorial Hospital, No. 12, Fu Chow Street, Taipei, Taiwan.

PATIENT DATA

Case No.	*Age*	*Sex*	*Diagnosis*	*Date of Operation*	*Problem on Standard Microlaryngeal Surgery*
1	45 y	F	Reinke's edema	Oct 1992	Limited neck extension
2	33 y	F	Vocal polyp	Nov 1992	Arrhythmia on forceful suspension
3	3 d	M	Vascular tumor, laryngomalacia	Dec 1992	Anatomic distortion due to large tumor
4	40 y	M	Vocal polyps	May 1993	Lesions mainly on tracheal surface of cords
5	43 y	F	Vocal nodules	Sept 1993	Limited neck extension
6	40 y	F	Vocal nodules	Feb 1994	Limited neck extension
7	62 y	M	Vocal cyst	July 1994	Short aryepiglottic folds
8	55 y	M	Carcinoma in situ	Dec 1994	Short, muscular neck
9	37 y	F	Polypoid corditis	Dec 1994	Limited neck extension
10	62 y	F	Vocal polyp	Feb 1995	Arrhythmia on forceful suspension
11	29 y	M	Vocal cyst	April 1995	Short, muscular neck
12	38 y	F	Vocal polyp	Nov 1995	Prominent incisors
13	35 y	M	Vocal polyps	July 1996	Short, muscular neck
14	36 y	M	Vocal polyp	Aug 1996	Short aryepiglottic folds

operation is carried out with microscissors, a microknife, or, most of the time, a laser. When the lesion is about to be detached from the surrounding tissue, a microforceps or the half cutting–half grasping microforceps is used to avoid specimen loss.

RESULTS

Operations on these 14 patients were all accomplished by this telescopic surgery technique. The specimens could be removed en bloc, as we prefer, except for 1 that occupied almost all the laryngeal and hypopharyngeal space. The postoperative voice was acceptable to the doctors, the patients, and the patients' families.

DISCUSSION

Possible factors that lead to exposure difficulty during conventional microscopic laryngeal surgery include a short, muscular neck, a small larynx, a short epiglottis, extension limitations of the cervical spine, etc.[1] We might exchange the general-purpose laryngoscope for a specially designed one, for example, a subglottiscope, anterior commissure scope, or some slim laryngoscope, in order to get access. Otherwise, we might apply overpressure on the patient's larynx. However, when we use these special-purpose slim laryngoscopes, the operative field is distorted or relatively small[2,8] and makes the operation and en bloc resection more difficult.

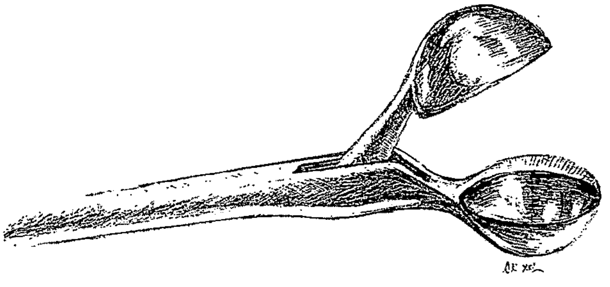


Fig 1. Half cutting–half grasping microforceps. Half circle of cup is made blunt to serve as part used for grasping.

On the other hand, when we try to use a larger laryngoscope to get a larger operative field, the resulting problem is overpressure on the larynx. That can lead to many complications such as mucosa laceration, arytenoid dislocation, reflex cardiac arrhythmia, bradycardia, asystole,[6] etc.

When we use the telescopic surgical technique, the above problems can be avoided or lessened. With the help of the angled telescopes, it is not necessary to fully expose the lesion site with the laryngoscope alone, so we can introduce and suspend the general-purpose laryngoscope gently and avoid overpressure on the larynx. Meanwhile, it is usually not necessary to use an endotracheal tube with a caliber as small as the one used in conventional laryngeal microsurgery. Either a 6.5-mm or a 7.0-mm tube is usually acceptable, because we can obtain views from different angles easily by this method. This will help to lower the anesthesia risk associated with a small-caliber endotracheal tube.

Areas that are difficult to view during conventional microscopic laryngeal examination, including the ventricles of Morgagni, the anterior commissure, and the inferior surface of the vocal cords and lesion, can be viewed clearly and directly by the telescopic method.[3-5] Andrea and Dias[5] have clearly described and illustrated the role in examination of a similar telescopic method.

Microscopic laryngeal surgery has been successfully extended to surgery of early laryngeal cancer and respiratory papillomatosis in recent years. For some transglottic lesions, it is possible to cut through

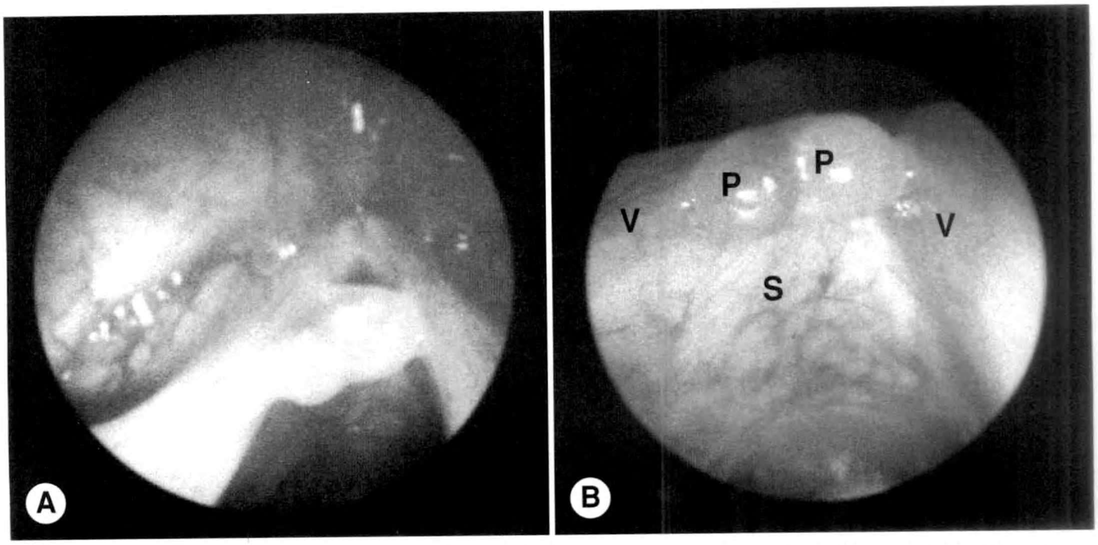


Fig 2. Views of lesions. A) (Case 12) Lesion, anterior commissure, and ventricle of Morgagni in 38-year-old woman with vocal polyp. Prominent incisors made exposure of anterior commissure difficult with conventional laryngeal microsurgery. B) (Case 4) View of lesions, via 70° telescope, on tracheal surface of vocal cords (V). Patient is 40-year-old man with vocal polyps (P), mainly on tracheal surface of vocal cord. S — subglottis.

the lesions, and theoretically, some tumor cells may drop into tumor vessels at this moment. Using the telescopic surgery method, we could observe the lesion not only from the upper surface but also from the inferior surface, that is, 3-D observation.[3,5] We could get a stereotactic image impression from this 3-D observation more easily than from conventional microscopic laryngeal surgery. So, the incision line could be determined with a better chance for en bloc excision with either a cold knife or a laser.

Loré[3] also developed a telescopic endolaryngeal surgery technique to substitute for standard microscopic laryngeal surgery. He also used different-angle telescopes to examine the lesion. After examination, he fixed the telescope to the channel of the optical forceps to do the operation. His technique is good for small lesions, biopsies, and foreign body removal. However, in managing larger, malignant lesions, there is a possibility of cutting through lesions.

Although there is an endoscopic holder commercially available,[7,8] we prefer to do this operation with the hands, because it is faster and more convenient in adjusting the views from one to another. Since this telescopic method is basically a 1-handed technique, some difficulty may be met with in the beginning.

The major disadvantage of this telescopic method comes from the fact that it is a 1-handed technique dealing with microscale lesions. So, it is better for the surgeon to be familiar with both endoscopic sinus surgery and standard laryngeal microsurgery before begining this method. Otherwise, specimen loss or unexpected trauma to the patient may occur, because the stability of the instruments during manipulation is more difficult to maintain than during conventional bimanual microsurgery. Practice is needed. However, if one is familiar with endoscopic sinus surgery, it should not take long to learn telescopic laryngeal surgery.

We should avoid overenthusiasm for this technique. Although the telescopic method can give us good access, there are still limitations. If we use force to employ it in patients with obvious limited neck extension or mouth opening, trauma may occur.

The image in conventional microscopic laryngeal surgery is well magnified. The detail of the upper surface of the lesion is clear through the operative microscope. How does the image obtained through the telescope compare? Thanks to the modern telescope, high-quality charge-coupled device, and monitor, we can also get enough magnification with the telescope for clinical use.

CONCLUSION

After some practice and with the modified instruments, telescopic laryngeal surgery can be performed smoothly. With 0° and 30° telescopes, we can perform most of the operations done by conventional microscopic laryngeal surgery. By the help of 70° and even 120° telescopes, we can do en bloc excision even better than by conventional microscopic methods. We consider this telescopic method to be a useful alternative to traditional microscopic laryngeal surgery and one more choice for surgeons.

REFERENCES

1. Vaughan CW. Vocal fold exposure in phonosurgery. J Voice 1993;7:189-94.

2. Kantor E, Berci G, Partlow E, Paz-Partlow M. A completely new approach to microlaryngeal surgery. Laryngoscope 1991;101:676-9.

3. Loré JM Jr. Telescopic endolaryngeal surgery. Ann Otol Rhinol Laryngol 1987;96:525-6.

4. Benjamin B. Diagnostic laryngology: adults and children. Philadelphia, Pa: WB Saunders, 1990.

5. Andrea M, Dias O. Atlas of rigid and contact endoscopy in microlaryngeal surgery. Philadelphia, Pa: Lippincott-Raven, 1995.

6. Strong MS, Vaughan CW, Mahler DL, Jaffe DR, Sullivan RC. Cardiac complications of microsurgery of the larynx: etiology, incidence and prevention. Laryngoscope 1974;84:908-20.

7. Wigand ME. Endoscopic surgery of the paranasal sinuses and anterior skull base. New York, NY: Thieme Medical Publishers, 1990.

8. Yanagisawa E, Horowitz JB, Yanagisawa K, Mambrino LJ. Comparison of new telescopic video microlaryngoscopic and standard microlaryngoscopic techniques. Ann Otol Rhinol Laryngol 1992;101:51-60.

* * *

MIDDLE EAR MECHANICS

The Second International Symposium on Middle Ear Mechanics in Research and Otosurgery will be held October 21-24, 1999, in Boston, Massachusetts. For information, contact Harvard MED-CME, PO Box 825, Boston, MA 02117; telephone (617) 432-1525; web site http://www.med.harvard.edu/conted/.

Ann Otol Rhinol Laryngol 108:1999

SPECIFIC IMMUNOGLOBULIN E, INTERLEUKIN-4, AND SOLUBLE VASCULAR CELL ADHESION MOLECULE–1 IN SERA IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

TATEO MASAMOTO, MD
YOSHIHIRO OHASHI, MD
YOSHIAKI NAKAI, MD
OSAKA, JAPAN

This study included 23 nonatopic volunteers and 84 patients with seasonal allergic rhinitis due to Japanese cedar pollen. Serum interleukin-4 (IL-4) and soluble vascular cell adhesion molecule–1 (sVCAM-1) in the patients were significantly higher than those in the nonatopic individuals, even outside of the pollen season. Both the good responders and the poor responders to antihistamine tablets showed significant increases in IL-4 and specific IgE during the pollen season, whereas such seasonal increases were not observed in the good responders to immunotherapy. Seasonal increases in IL-4 were significantly correlated with those of specific IgE. However, seasonal increases in sVCAM-1 were not significant. Seasonal increases in sVCAM-1 were not significantly different between the good responders and the poor responders to pharmacotherapy or immunotherapy. In conclusion, serum IL-4 and sVCAM-1 are increased in patients with seasonal allergic rhinitis, even outside of the pollen season; this finding might suggest underlying preponderant in vivo activation of T helper cell–2–like cells and inflammatory events in seasonal allergic rhinitis. A seasonal increase in IL-4 in sera might be at least partly involved in the seasonal increase in specific IgE in sera. Immunotherapy's inhibitory effect on IL-4 production and specific IgE response might be one of its working mechanisms.

KEY WORDS — immunotherapy, interleukin-4, seasonal allergic rhinitis, soluble vascular cell adhesion molecule–1, specific IgE.

INTRODUCTION

Airway allergic inflammation is characterized by preferential eosinophil and T cell recruitment with relatively modest neutrophil recruitment.[1] Migration of leukocytes is controlled by the interaction of cell surface adhesion molecules between leukocytes and vascular endothelial cells.[2-4] In vitro studies have shown that eosinophils utilize intercellular adhesion molecule–1 (ICAM-1), vascular cell adhesion molecule–1 (VCAM-1), and E-selectin–dependent pathways to adhere to vascular endothelial cells. By contrast, neutrophils cannot utilize VCAM-1–dependent pathways, because of the lack of very late antigen–4 (VLA-4) expression on their cell surface.[5] In asthmatics, the endothelial expression of VCAM-1 was positively correlated with the number of eosinophils, but not neutrophils, in the bronchial submucosa.[6] Nakajima et al[7] found that in vivo blocking of VCAM-1 and VLA-4, but not of ICAM-1 and lymphocyte function–associated antigen–1 (LFA-1), prevented antigen-induced eosinophil infiltration into the mouse trachea, and that VCAM-1–VLA-4 interaction is functionally predominant over ICAM-1–LFA-1 interaction in controlling antigen-induced T cell recruitment into the tissue. To take these lines of evidence together, the induction of VCAM-1 expression on the endothelium may play a central part in selective recruitment of eosinophils and T cells into allergic inflammatory lesions.

Soluble VCAM-1 (sVCAM-1) has been identified in the peripheral blood of normal subjects and patients with various diseases.[8,9] Soluble VCAM-1 is released by activated endothelial cells in culture and is detectable in sera[10]; however, there is limited published information on the clinical role of sVCAM-1 in the blood.[8] The expression of adhesion molecules on endothelial cells has been shown to be upregulated in vitro by various cytokines. In particular, interleukin-4 (IL-4), which plays the most critical role in the switching of B lymphocytes to produce IgE[11,12] and seems to be of critical importance in the development of allergic diseases, could increase expression of VCAM-1 on endothelial cells.[13] Thus, IL-4 may be involved in eosinophil adhesion and selective eosinophil infiltration in allergic inflammation.

Our study is aimed at elucidating whether the serum levels of sVCAM-1 and IL-4 in patients with seasonal allergic rhinitis are higher than those in nonatopic healthy volunteers, whether their serum concentrations are increased in response to natural provocation, and whether the seasonal increase in IL-4

From the Department of Otolaryngology, Osaka City University Medical School, Osaka, Japan. Supported by the Ministry of Education, Science and Culture of Japan (Grant-in-Aid for Scientific Research 07671878).

CORRESPONDENCE — Yoshihiro Ohashi, MD, Dept of Otolaryngology, Osaka City University Medical School, 1-4-3 Asahimachi, Abeno, Osaka 545-8585, Japan.

in sera is involved in the seasonal increase in sVCAM-1 in sera.

MATERIALS AND METHODS

Patients. This study included 84 adult patients (age range 18 to 59 years) with seasonal allergic rhinitis due to Japanese cedar (*Cryptomeria japonica*) pollen who gave informed consent to the participation. All the patients were selected from our outpatients who completely satisfied the following conditions before treatment: 1) a well-documented history of typical Japanese cedar pollinosis but no history of asthma and no nasal symptoms outside of the cedar pollen season, 2) a positive skin test to Japanese cedar pollens, 3) positive nasal provocation to the pollen, and 4) eosinophilia in nasal smears during the cedar pollen season. The patients were divided into a medication group and an immunotherapy group according to their treatment background. None of the patients of the medication group had previously been treated with immunotherapy or was receiving steroid treatment. The patients of the immunotherapy group had had variable periods (mean 5.4 ± 4.1 years; range 1 to 15 years) of immunotherapy with Japanese cedar pollen (Torii Co, Ltd, Tokyo, Japan).

To serve as controls, 23 nonallergic healthy volunteers (age range 25 to 64 years; nonatopic group) were chosen on the basis of the following criteria: 1) a negative history for allergic diseases, 2) no physical findings consistent with atopic diseases, and 3) negative serum IgE antibodies specific to the major allergens in Japan, such as house dust mite, Japanese cedar pollen, ragweed, Japanese cypress pollen, and mold.

Study Design. The period for pollination of Japanese cedar in 1996 was from the first week of February to the second week of April. The 23 patients of the medication group were treated with antihistamine tablets alone from the last week of January to the end of April. The 61 patients of the immunotherapy group continued to receive scheduled subcutaneous injections of a maintenance dose. The patients of the immunotherapy group were allowed to take rescue medications (antihistamine tablets) during the pollen season, if necessary.

Venous blood was collected twice from each patient, before the cedar pollen season of 1996 (from December 1995 to January 1996) and during the cedar pollen season of 1996 (first week of April 1996), to determine the cedar pollen–specific IgE, IL-4, and sVCAM-1 in sera. Venous blood was also collected outside of the pollen season from the nonatopic group to determine cedar pollen–specific IgE, IL-4, and sVCAM-1 in sera.

Determination of Serum Specific IgE, IL-4, and sVCAM-1. Specific IgE antibodies, IL-4, and sVCAM-1 in sera were determined at the same time. Immunoglobulin E specific to Japanese cedar pollen was measured by the lumiward immunoassay system.[14] Interleukin-4 was measured with our chemiluminescent enzyme-linked immunosorbent assay (ELISA).[15] The method employed is capable of detecting 0.4 to 100 pg/mL of IL-4, and does not measure the presence of other cytokines. Soluble VCAM-1 was determined by a sandwich ELISA (ELISA kit from R & D System, Minneapolis, Minn).

The seasonal increase rate in specific IgE, IL-4, or sVCAM-1 in sera following pollen exposure was calculated with the following formula: Seasonal increase rate (%) = (values during pollen season – values before pollen season)/(values before pollen season) × 100.

Clinical Evaluation. Clinical evaluation was performed for each patient, based on our criteria using daily symptom diary cards, during the first week of April in 1996. The details of the method employed in this study have been described elsewhere.[16,17] In brief, all patients were asked to complete daily symptom diary cards in the 7 days before clinical assessment. The average daily scores of the sum total of the 3 nasal symptom scores (sneezing, rhinorrhea, and obstruction) were used as total symptom scores (maximum 9). According to their total symptom scores, the patients of the medication group were divided into good responders, whose total symptom scores were 0 to 2, and poor responders, whose total symptom scores were 3 to 9. The patients of the immunotherapy group were also divided into good responders, whose total symptom scores were 0 to 2 without rescue medication, and poor responders, whose total symptom scores were 3 to 9 and who needed rescue medication to control their nasal symptoms.

Statistical Analysis. For comparison of data between groups, a Mann-Whitney U-test was used. For comparison of the paired values within a group, Wilcoxon's signed-rank test was used. Significant differences were accepted in each analysis when $p < .05$. Spearman's correlation coefficient (r_s) was calculated to analyze possible correlation between 2 different parameters, and significant correlation was accepted when $p < .05$ according to the Spearman's rank correlation analysis.

RESULTS

Serum levels and seasonal increase rates of specific IgE, IL-4, and sVCAM-1 are summarized in Tables 1-3.

TABLE 1. SPECIFIC IMMUNOGLOBULIN E

	Before Pollen Season (U/mL)	*During Pollen Season (U/mL)*	*Seasonal Increase Rate (%)*
Medication group (n = 23)	24.92 ± 14.95	39.90 ± 24.78	61.1 ± 54.9
Good responders (n = 11)	24.02 ± 15.91	36.26 ± 28.05	44.1 ± 53.7
Poor responders (n = 12)	25.75 ± 14.67	43.25 ± 22.06	76.7 ± 53.5
Immunotherapy group (n = 61)	21.73 ± 17.34	24.01 ± 18.80	13.7 ± 26.6
Good responders (n = 31)	21.41 ± 12.16	21.16 ± 12.35	−1.2 ± 8.9
Poor responders (n = 30)	22.07 ± 21.65	26.96 ± 23.58	29.2 ± 29.9
Nonatopic group (n = 23)	0 ± 0		

Data are mean ± SD.

Specific IgE, IL-4, and sVCAM-1 Before Pollen Season. Immunoglobulin E specific to cedar pollen was not detected in any individual of the nonatopic group. Serum levels of IL-4 in the medication group and the immunotherapy group before the pollen season were significantly higher than those in the nonatopic group (nonatopic group versus medication group, p = .0071; nonatopic group versus immunotherapy group, p = .0043). Serum levels of sVCAM-1 in the medication group and the immunotherapy group before the pollen season were significantly higher than those in the nonatopic group (nonatopic group versus medication group, p = .0023; nonatopic group versus immunotherapy group, p = .0008). However, specific IgE, IL-4, and sVCAM-1 before the pollen season were not significantly different between the medication group and the immunotherapy group (specific IgE, p = .2364; IL-4, p = .4183; sVCAM-1, p = .7903).

Specific IgE, IL-4, and sVCAM-1 During Pollen Season. Serum levels of IL-4 in the medication group and the immunotherapy group during the pollen season were significantly higher than serum levels of IL-4 in the nonatopic group (nonatopic group versus medication group, p = .0003; nonatopic group versus immunotherapy group, p = .0010). Serum levels of sVCAM-1 in the medication group and the immunotherapy group during the pollen season were significantly higher than those in the nonatopic group (nonatopic group versus medication group, p = .0092; nonatopic group versus immunotherapy group, p < .0001).

Seasonal Changes in Specific IgE, IL-4, and sVCAM-1. Serum levels of specific IgE and IL-4 during the pollen season were significantly higher than those before the pollen season, in both the medication group (specific IgE, p = .0001; IL-4, p = .0008) and the immunotherapy group (specific IgE, p = .0037; IL-4, p = .0005). However, serum levels of sVCAM-1 were not significantly changed in either the medication group (p = .8552) or the immunotherapy group (p = .1135).

The seasonal increase rates in sVCAM-1 were not significantly different between the medication group and the immunotherapy group (p = .3696). On the other hand, both the seasonal increase rate in specific IgE and the seasonal increase rate in IL-4 were significantly larger in the medication group than in the immunotherapy group (specific IgE, p < .0001; IL-4, p = .0001).

Clinical Effect in Medication Group. The numbers of good responders and poor responders to antiallergic pharmacotherapy were 11 and 12, respectively. Specific IgE, IL-4, and sVCAM-1 before the pollen season were not significantly different between the good responders and the poor responders (specific IgE, p = .5369; IL-4, p = .1637; sVCAM-1, p = .1659). Specific IgE and IL-4 were significantly increased during the pollen season in both the good responders (specific IgE, p = .0144; IL-4, p = .0049) and the poor responders (specific IgE, p = .0029;

TABLE 2. INTERLEUKIN-4

	Before Pollen Season (pg/mL)	*During Pollen Season (pg/mL)*	*Seasonal Increase Rate (%)*
Medication group (n = 23)	2.04 ± 1.11	3.45 ± 2.46	57.4 ± 44.6
Good responders (n = 11)	1.68 ± 0.97	2.48 ± 1.76	44.2 ± 31.8
Poor responders (n = 12)	2.38 ± 1.16	4.33 ± 2.74	69.6 ± 52.2
Immunotherapy group (n = 61)	1.99 ± 1.57	2.33 ± 1.90	19.7 ± 44.0
Good responders (n = 31)	2.06 ± 1.72	2.01 ± 1.77	−2.4 ± 18.3
Poor responders (n = 30)	1.92 ± 1.41	2.67 ± 1.99	42.4 ± 51.0
Nonatopic group (n = 23)	1.18 ± 1.26		

Data are mean ± SD.

TABLE 3. SOLUBLE VASCULAR CELL ADHESION MOLECULE–1

	Before Pollen Season (ng/mL)	*During Pollen Season (ng/mL)*	*Seasonal Increase Rate (%)*
Medication group (n = 23)	594.1 ± 137.6	589.9 ± 150.7	–0.1 ± 13.9
Good responders (n = 11)	639.6 ± 100.5	648.5 ± 146.0	1.3 ± 15.1
Poor responders (n = 12)	552.3 ± 157.2	536.3 ± 139.5	–1.4 ± 13.2
Immunotherapy group (n = 61)	589.5 ± 145.4	612.5 ± 129.8	6.4 ± 19.1
Good responders (n = 31)	579.4 ± 151.4	608.1 ± 135.0	7.5 ± 20.0
Poor responders (n = 30)	599.9 ± 140.8	617.1 ± 126.4	5.2 ± 18.5
Nonatopic group (n = 23)	493.4 ± 58.3		

Data are mean ± SD.

IL-4, p = .0033; Figs 1 and 2). Neither the good responders nor the poor responders showed significant changes in sVCAM-1 during the pollen season (good responders, p = .7221; poor responders, p = .8138; Fig 3). The seasonal increase rates in specific IgE, IL-4, and sVCAM-1 were not significantly different between the good responders and the poor responders (IgE, p = .2813; IL-4, p = .2952; sVCAM-1, p = .5383).

Clinical Effect in Immunotherapy Group. The numbers of good responders and poor responders to immunotherapy were 31 and 30, respectively. Specific IgE, IL-4, and sVCAM-1 before the pollen season were not significantly different between the good responders and the poor responders (specific IgE, p = .3671; IL-4, p = .9885; sVCAM-1, p = .5161). In the good responders, neither specific IgE nor IL-4 was significantly changed during the pollen season (specific IgE, p = .7725; IL-4, p = .4474; Figs 1 and 2). By contrast, both specific IgE and IL-4 were significantly increased during the pollen season in the poor responders (specific IgE, p = .0004; IL-4, p < .0001; Figs 1 and 2). Neither the good responders nor the poor responders showed significant changes in sVCAM-1 during the pollen season (good responders, p = .2802; poor responders, p = .3820; Fig 3). Both the seasonal increase rate in specific IgE and the seasonal increase rate in IL-4 were significantly lower in the good responders than in the poor responders (specific IgE, p < .0001; IL-4, p < .0001). However, the seasonal increase rate in sVCAM-1 was not significantly different between the good responders and the poor responders (p = .7729).

Correlation Analysis in Medication Group. A significant correlation was observed between the seasonal increase rate in specific IgE and the seasonal increase rate in IL-4 (rs = .812, p = .0001; Fig 4). However, neither the seasonal increase rate in specific IgE nor the seasonal increase rate in IL-4 was significantly correlated with the seasonal increase rate in sVCAM-1 (IgE versus sVCAM-1, rs = .158, p = .4596; IL-4 versus sVCAM-1, rs = –.014, p = .9464).

Correlation Analysis in Immunotherapy Group. A significant correlation was observed between the seasonal increase rate in specific IgE and the seasonal increase rate in IL-4 (rs = .760, p <.0001, Fig 4). However, neither the seasonal increase rate in specific IgE nor the seasonal increase rate in IL-4 was significantly correlated with the seasonal increase rate in sVCAM-1 (IgE versus sVCAM-1, rs = –.233, p = .0705; IL-4 versus sVCAM-1, rs = –.055, p = .6654). Both the seasonal increase rate in specific IgE and the seasonal increase rate in IL-4 were inversely correlated with the duration of immunotherapy (IgE, rs = –.402, p = .0013; IL-4, rs = –.271, p = .0285), but the seasonal increase rate in sVCAM-1 was not significantly correlated with the duration of immunotherapy (rs = .143, p = .2930).

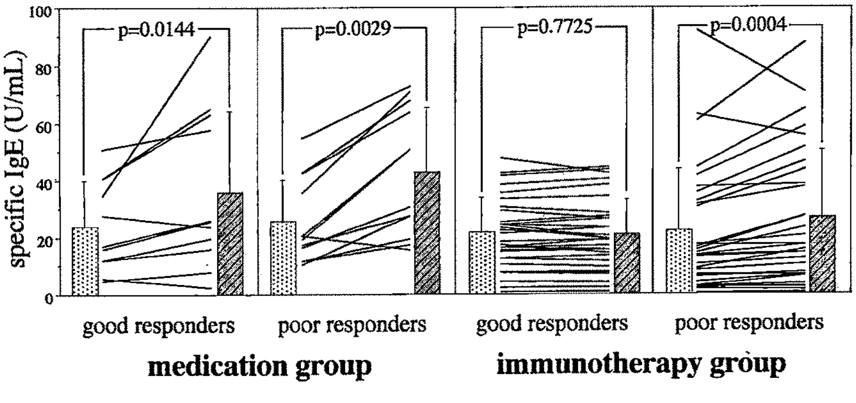


Fig 1. Specific IgE levels before (dotted bars) and during (dark, striped bars) pollen season. Levels of specific IgE during pollen season are significantly higher than those before pollen season in good responders of medication group, poor responders of medication group, and poor responders of immunotherapy group. However, levels of specific IgE during pollen season are not significantly different from those before pollen season in good responders of immunotherapy group.

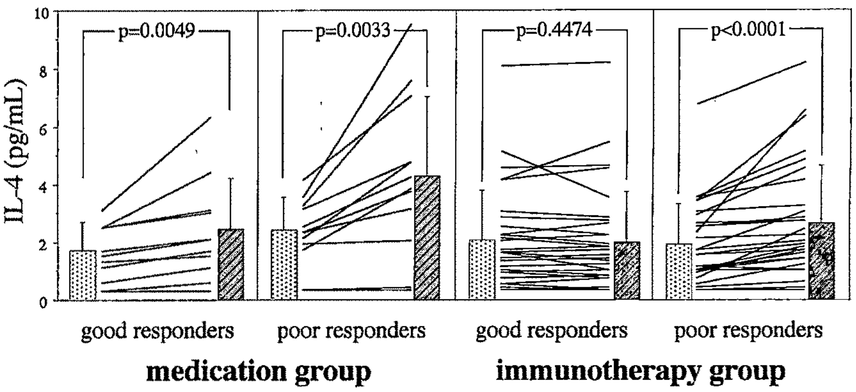


Fig 2. Interleukin-4 (IL-4) levels before (dotted bars) and during (dark, striped bars) pollen season. Levels of IL-4 during pollen season are significantly higher than those before pollen season in good responders of medication group, poor responders of medication group, and poor responders of immunotherapy group. However, levels of IL-4 during pollen season are not significantly different from those before pollen season in good responders of immunotherapy group.

DISCUSSION

Atopic disease is associated with a primary abnormality of T cell function,[18] and serum levels of IL-4 were elevated in atopic individuals compared with nonatopic controls.[15,19,20] If serum levels of IL-4 in patients with seasonal allergic rhinitis are elevated even outside of the pollen season, it might be evidence for an underlying preponderant in vivo activation of T helper cell–2 (Th2)–like cells in peripheral blood in seasonal allergic rhinitis. Zangrilli et al[21] found a large increase in sVCAM-1 in the bronchoalveolar lavage fluid from atopic asthmatics after segmental allergen challenge, and the level was correlated with eosinophil influx and the late phase response. Similarly, sVCAM-1 in sera might represent ongoing allergic inflammation. If the levels of sVCAM-1 vary between atopic and nonatopic subjects, then this variance would be of diagnostic use and of interest in the investigation of allergic inflammation.

Thus, the primary aim of this study was to elucidate whether the serum levels of IL-4 and sVCAM-1 during and/or outside of the pollen season in patients with seasonal allergic rhinitis were significantly different from those in nonatopic controls. In this study, all the subjects were 18 or more years old, because serum sVCAM-1 in children might decrease with age.[9] Both of the patient groups — the medication group and the immunotherapy group — demonstrated significantly higher levels of IL-4 and sVCAM-1 before, as well as during, the pollen season than did the nonatopic group. It is therefore likely that measurement of IL-4 and sVCAM-1 concentrations in sera will be of some diagnostic use. In particular, higher levels of IL-4 and sVCAM-1, even outside of the pollen season, may represent underlying preponderant in vivo activation of Th2-like cells and underlying inflammatory events in patients with seasonal allergic rhinitis. Montefort et al[22] have not been able to show a significant difference in the serum concentrations of sVCAM-1 between normal subjects and subjects with well-controlled asthma. In this respect, our present results are not consistent with their data.

The Japanese cedar pollinates heavily in the early spring, and there is no significant interference with other pollens.[23] Therefore, Japanese cedar pollination could provide an excellent in vivo model for investigating the immunologic and inflammatory changes in response to natural provocation to the allergen. Seasonal rises in specific IgE in sera in patients with pollen-sensitive allergy have been well established. Indeed, serum levels of specific IgE during the pollen season were significantly higher than those before the pollen season, in both the medication group ($p = .0001$) and the immunotherapy group ($p = .0037$). Since Th2-like cell–derived IL-4 plays a key role in inducing and increasing the generation of both primary polyclonal and secondary specific

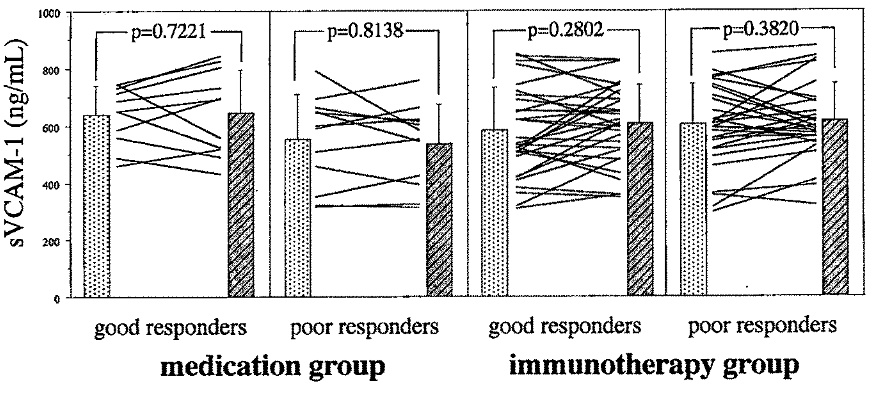


Fig 3. Soluble vascular cell adhesion molecule–1 (sVCAM-1) levels before (dotted bars) and during (dark, striped bars) pollen season. None of subgroups (good responders of medication group, poor responders of medication group, good responders of immunotherapy group, and poor responders of immunotherapy group) show significant increase in sVCAM-1 levels during pollen season as compared to before pollen season.

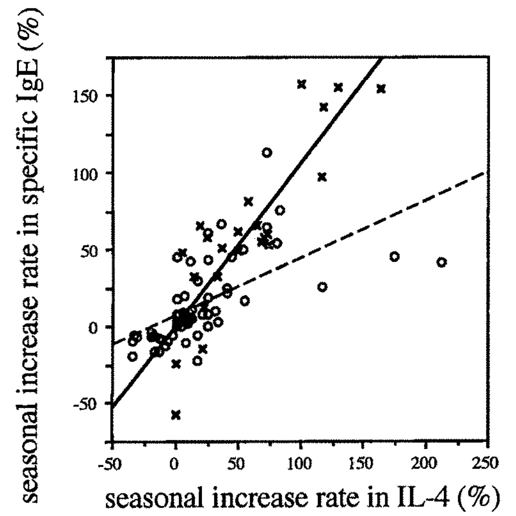


Fig 4. Seasonal increase rate in specific IgE versus seasonal increase rate in IL-4. Seasonal increase rate in specific IgE is significantly correlated with seasonal increase rate in IL-4, in both medication group (crosses and solid line; rs = .812, p = .0001) and immunotherapy group (open circles and broken line; rs = .760, p < .0001).

IgE responses by B lymphocytes,[11,12] IL-4 seems to be involved in seasonal rises in specific IgE in seasonal allergic rhinitis. Seasonal rises in specific IgE in sera might be partly the result of seasonal rises in IL-4 in sera. Similarly, the serum levels of sVCAM-1 in patients with seasonal allergic rhinitis might be increased in response to natural exposure to the pollens and might be, at least in part, involved in seasonal aggravation of allergic inflammation. Interleukin-4 could also exert an important regulatory effect on the expression of VCAM-1 on the endothelial cells.[13] Thus, our second purpose was to examine a possible seasonal increase in IL-4 and sVCAM-1 in sera in patients with seasonal allergic rhinitis and to determine a possible correlation among the seasonal rises in specific IgE, IL-4, and sVCAM-1 in sera.

In the meantime, immunotherapy is an effective form of treatment for seasonal allergic rhinitis.[24,25] In the present study, immunotherapy was clinically effective in approximately half of the patients. We previously demonstrated that an elevation of serum IL-4 in perennial allergic rhinitis could be down-regulated by prolonged immunotherapy, and this decrease was significantly correlated with a decrease in specific IgE in sera.[15] Similarly, pollen immunotherapy might modulate a seasonal change in specific IgE and IL-4 in sera. Our study was therefore designed to investigate possible modification of seasonal changes in specific IgE, IL-4, and sVCAM-1 in sera.

In the patients treated with antihistamine tablets, but not with immunotherapy, IL-4 in sera was significantly increased during the pollen season rather than before the season, and the seasonal increase rate in IL-4 was significantly correlated with the seasonal increase rate in specific IgE. Our data have therefore suggested that natural provocation could increase serum IL-4 and that a seasonal increase in IL-4 might be at least partly involved in the seasonal increase in specific IgE. Both the good responders and the poor responders of the medication group demonstrated significant increases in specific IgE and IL-4 during the pollen season. Since our study includes no untreated control patients, we cannot conclusively refer to whether antihistamine medication could influence the seasonal increase in specific IgE and IL-4. However, our data have demonstrated that the magnitude of the clinical effect of antihistamines is independent of the increase in specific IgE and IL-4, because the seasonal increase rates in specific IgE and IL-4 were not different between the good and poor responders to antihistamines.

A seasonal increase in specific IgE and IL-4 in sera and a significant correlation between their increase rates were also found in the patients treated with immunotherapy, but the increase rates in specific IgE and IL-4 in the immunotherapy group were significantly smaller than those in the medication group. Immunotherapy is likely to suppress seasonal increases in specific IgE and IL-4, as opposed to antiallergic pharmacotherapy. Of more interest, a seasonal increase in specific IgE and IL-4 was significant in the poor responders, but not significant in the good responders to immunotherapy. Moreover, the seasonal increase rates in specific IgE and IL-4 were significantly smaller in the good responders than in the poor responders to immunotherapy. Taking these lines of evidence together, the suppression of the seasonal rise in specific IgE and IL-4 by immunotherapy is likely to be implicated in the clinical effect. This inhibitory effect on specific IgE response and IL-4 production during the pollen season might be one of the working mechanisms of immunotherapy. In this study, the seasonal increase rates in both specific IgE and IL-4 were inversely correlated with the duration of immunotherapy; this finding indicates that this inhibitory effect becomes more apparent as immunotherapy proceeds.

Neither the medication group nor the immunotherapy group showed an increase in sVCAM-1 in sera in response to natural exposure to pollens. The seasonal increase rates in sVCAM-1 were not significantly different between the good responders and the poor responders to pharmacotherapy and immunotherapy. The seasonal increase rates in sVCAM-1 were not correlated with the seasonal increase rates in specific IgE or IL-4. Therefore, our study did not support any important pathogenic or clinical role for sVCAM-1 in sera in patients with seasonal allergic rhinitis. All we can conclude from the present study is that sVCAM-1 levels in sera are higher in patients with seasonal allergic rhinitis than in nonatopic healthy volunteers, even outside of the pollen season, and that maintained higher levels of sVCAM-1 might be implicated in underlying inflammatory events in seasonal allergic rhinitis.

In conclusion, we have demonstrated that serum concentrations of IL-4 and sVCAM-1 are increased in patients with seasonal allergic rhinitis, even outside of the pollen season, and this finding might suggest underlying preponderant in vivo activation of Th2-like cells and inflammatory events in patients with seasonal allergic rhinitis. Our data have suggested that a seasonal increase in IL-4 might be at least partly involved in the seasonal increase in specific IgE, and that the suppression of the seasonal rise in specific IgE and IL-4 by immunotherapy is likely to be implicated in the clinical effect as one of the working mechanisms. However, our study could not find a significant increase in sVCAM-1 in sera during the pollen season. In addition, no significant association was found between the seasonal increase in serum sVCAM-1 and the clinical response to pharmacotherapy or immunotherapy.

ACKNOWLEDGMENTS — The authors acknowledge the important technical assistance of Yoshiharu Ohno, MD, Hirokazu Sakamoto, MD, Akifumi Kato, MD, Ayaki Tanaka, MD, Yasushi Kakinoki, MD, and Yushi Washio, MD, in the Department of Otolaryngology, Osaka City University Medical School.

REFERENCES

1. Kay AB. Asthma and inflammation. J Allergy Clin Immunol 1991;87:893-910.

2. Calderon E, Lockey RF. A possible role for adhesion molecules in asthma. J Allergy Clin Immunol 1992;90:852-65.

3. Resnick MB, Weller PF. Mechanisms of eosinophil recruitment. Am J Respir Cell Mol Biol 1993;8:349-55.

4. Bochner BS, Schleimer RP. The role of adhesion molecules in human eosinophil and basophil recruitment. J Allergy Clin Immunol 1994;94:427-38.

5. Bochner BS, Luscinskas FW, Gimbrone MA, et al. Adhesion of human basophils, eosinophils, and neutrophils to interleukin-1–activated human vascular endothelial cells: contributions of endothelial cell adhesion molecules. J Exp Med 1991; 173:1553-6.

6. Fukuda T, Fukushima Y, Numano T, et al. Role of interleukin-4 and vascular cell adhesion molecule–1 in selective eosinophil migration into the airways in allergic asthma. Am J Respir Cell Mol Biol 1996;14:84-94.

7. Nakajima H, Sano H, Nishimura T, Yoshida S, Iwamoto I. Role of vascular cell adhesion molecule 1/very late activation antigen 4 and intercellular adhesion molecule 1/lymphocyte function–associated antigen 1 interactions in antigen-induced eosinophil and T cell recruitment into the tissue. J Exp Med 1994;179:1145-54.

8. Gearing AJH, Newman W. Circulating adhesion molecules in disease. Immunol Today 1993;14:506-12.

9. Nash MC, Wada AM, Shah V, Dillon MJ. Normal levels of soluble E-selectin, soluble intercellular adhesion molecule–1 (sICAM-1), and soluble vascular cell adhesion molecule–1 (sVCAM-1) decrease with age. Clin Exp Immunol 1996;103: 167-70.

10. Mason JC, Kapahi P, Wellicome SM, Lebranchu Y, Yarwood H, Haskard DO. Detection of a circulating form of VCAM-1: raised levels in rheumatoid arthritis and systemic lupus erythematosus and lack of correlation with levels of circulating ICAM-1 [Abstract]. Br J Rheumatol 1992;31(suppl 2):90.

11. Prete GD, Maggi E, Parronchi P, et al. IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. J Immunol 1988;140:4193-8.

12. Leung DYM, Geha RS. Regulation of the human IgE antibody response. Int Rev Immunol 1987;2:75-91.

13. Schleimer RP, Sterbinsky SA, Kaiser J, et al. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium: association with expression of VCAM-1. J Immunol 1992;148:1086-92.

14. Ohashi Y, Ohno Y, Okamoto H, et al. Clinical evaluation of lumiward immunoassay system for the measurement of Japanese cedar pollen–specific IgE antibodies. Pract Otol (Kyoto) 1996;89:575-81.

15. Ohashi Y, Nakai Y, Sakamoto H, et al. Serum level of interleukin-4 in patients with perennial allergic rhinitis during allergen-specific immunotherapy. Scand J Immunol 1996;43: 680-6.

16. Ohashi Y, Nakai Y, Sakamoto H, et al. Serum levels of soluble interleukin-2 receptor in patients with perennial allergic rhinitis before and after immunotherapy. Ann Allergy Asthma Immunol 1996;77:203-8.

17. Ohashi Y, Nakai Y, Okamoto H, et al. Significant correlation between symptom score and IgG4 antibody titer following long-term immunotherapy for perennial allergic rhinitis. Ann Otol Rhinol Laryngol 1997;106:483-9.

18. Borres MP, Einarsson R, Björkstén B. Serum levels of interleukin-4, soluble CD23 and IFN-γ in relation to the development of allergic disease during the first months of life. Clin Exp Allergy 1995;25:543-8.

19. Matsumoto T, Miike T, Yamaguchi K, Murakami M, Kawabe T, Yodoi J. Serum levels of soluble IL-2 receptor, IL-4 and IgE-binding factors in childhood allergic diseases. Clin Exp Immunol 1991;85:288-92.

20. Reddy MM, Weissman AM, Mazza DS, Meriney DK, Johns M. Circulating elevated levels of soluble CD23, interleukin-4, and $CD20^+CD23^+$ lymphocytes in atopic subjects with elevated serum IgE concentrations. Ann Allergy 1992;69:131-4.

21. Zangrilli JG, Shaver JR, Cirelli RA, et al. sVCAM-1 levels after segmental antigen challenge correlate with eosinophil influx, IL-4 and IL-5 production, and the late phase response. Am J Respir Crit Care Med 1995;151:1346-53.

22. Montefort S, Lai CKW, Kapahi P, et al. Circulating adhesion molecules in asthma. Am J Respir Crit Care Med 1994;149: 1149-52.

23. Ohashi Y, Nakai Y, Kakinoki Y, et al. The effect of immunotherapy on the serum levels of eosinophil cationic protein in seasonal allergic rhinitis. Clin Otolaryngol 1997;22:100-5.

24. Pence HL, Mitchell DQ, Greely RL. Immunotherapy for mountain cedar pollinosis: a double-blind controlled study. J Allergy Clin Immunol 1976;58:39-50.

25. Lichtenstein LM, Norman PS, Winkenwerder WL. A single year of immunotherapy for ragweed hay fever: immunologic and clinical studies. Ann Intern Med 1971;75:663-71.

≈

INTERNATIONAL MEETING ON OTOLOGY

The International Meeting on Otology of the Jean Causse Ear Clinic will be held June 5, 1999, in Béziers, France. For more information, please contact Robert Vincent, MD, Jean Causse Ear Clinic, Traverse de Béziers, 34440 Colombiers, France; telephone (33) 4-67-35-62-62; fax (33) 4-67-35-62-00.

Ann Otol Rhinol Laryngol 108:1999

DIAGNOSTIC AND THERAPEUTIC APPROACH TO MIGRATING FOREIGN BODIES

LINCOLN W. J. CHEE, MD, FRCS DHARAMBIR S. SETHI, MD, FRCS

SINGAPORE

Ingested foreign bodies are the commonest otolaryngological emergency in Singapore and other parts of Southeast Asia. One of the uncommon complications of ingested foreign bodies is migration, which has the potential to cause morbidity and mortality. A retrospective study of 24 patients presenting from 1990 to 1996 at Singapore General Hospital was done to evaluate the presentation, investigation, and diagnosis of migrated foreign bodies. Of interest, most patients had ingested foreign bodies within 24 hours. All the migrated foreign bodies were linear, sharp fish bones. Migration is said to have occurred in the presence of positive neck radiography and negative rigid esophagoscopy. Computed tomography is the investigation of choice to confirm migration. All patients had neck exploration, and factors for successful outcome are discussed. This is the largest series in the literature to date.

KEY WORDS — computed tomography, ingested foreign bodies, migration, neck exploration technique, presentation.

INTRODUCTION

Ingested foreign bodies remain the commonest otolaryngological emergency in Singapore and other parts of Southeast Asia. Fish bones constitute more than 85% of all foreign bodies, and most are impacted at the tonsils or base of the tongue.[1] Fortunately, most of these can be removed with minimal morbidity. Retained foreign bodies in the esophagus, however, can result in complications such as retropharyngeal abscess (Fig 1), perforation of the esophagus, or vascular complications, all of which can increase morbidity or even cause death. Rarely, the foreign body can migrate extraluminally and present in the subcutaneous tissue of the neck (Fig 2) or be embedded in the surrounding tissues such as the thyroid gland.[2] These situations have been reported in the medical literature as case reports, with no attempts at analysis or suggestion of management protocols. We review 24 cases of migrated foreign bodies in the aerodigestive tract that were treated over the 6-year period between 1990 and 1996 at Singapore General Hospital and share our experience in the management of this difficult clinical problem.

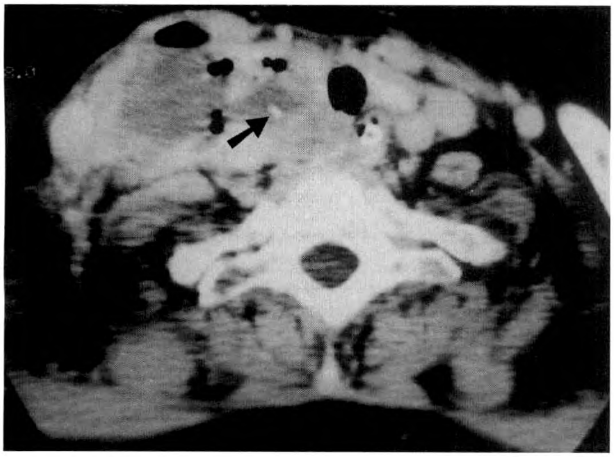


Fig 1. Migrated foreign body (arrow) in retropharyngeal and parapharyngeal neck abscess.

MATERIALS AND METHODS

All 24 patients had exploration of the neck for migrated foreign bodies. Migration is said to have occurred in the event of a negative rigid esophagoscopy and in the presence of a foreign body in or outside of the upper digestive tract on computed tomography (CT). A retrospective examination of the case notes was carried out to record demographic characteristics, mode of presentation, clinical and radiologic findings on admission, operative findings, techniques employed, and patient outcome.

RESULTS

The patients had a wide age range (18 to 82 years,

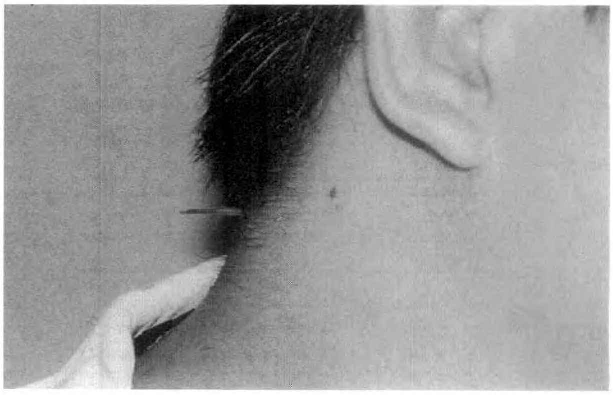


Fig 2. Migrated fish bone in skin of neck.

From the Department of Otolaryngology, Singapore General Hospital, Singapore, Singapore.

CORRESPONDENCE — Lincoln W. J. Chee, MD, FRCS, Dept of Otolaryngology, Singapore General Hospital, Outram Road, Singapore 169608.

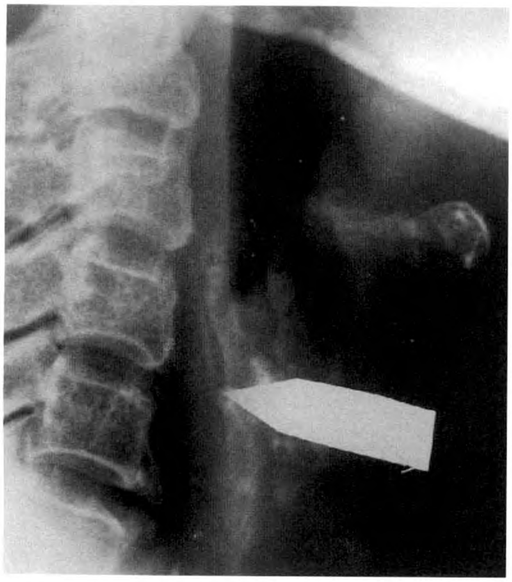


Fig 3. Lateral neck radiograph with presence of foreign body (white arrow).

mean 42.6) and no significant sexual predilection (13 men, 11 women). Twenty were Chinese, 2 Malay, and 2 Indian. All the patients gave a history of foreign body ingestion and ipsilateral neck pain. Only 1 patient presented with fever and a neck abscess. Surprisingly, most (18) of the patients had ingested the foreign body less than a day earlier. Three had ingested it several days earlier, two "weeks" earlier, and one 2 months earlier. A water drinking test and a laryngeal rub were not found to be diagnostic in these patients, unlike those with impacted foreign bodies.[3]

Radiologic Investigations. All the patients had an initial lateral neck radiograph, and 23 were positive for an ingested foreign body (Fig 3). The only exception showed the presence of a retropharyngeal abscess obscuring the underlying foreign body. Repeat lateral neck radiography did not alter any of the original findings. More significantly, all the migrated foreign bodies were positively identified on 3-mm axial cuts of a CT scan with soft tissue windows (Fig 4). A nasogastric tube was sometimes employed to keep the esophagus from collapsing. This helped to differentiate a foreign body embedded in the anterior esophageal wall from one in the posterior wall. Barium swallow studies were not considered useful in the management of suspected migration, as CT scans are readily available in our hospital and have less radiation exposure.[4]

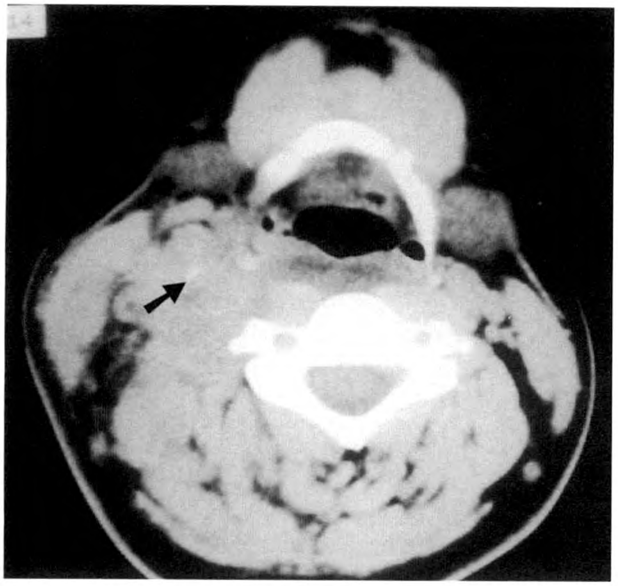


Fig 4. Axial computed tomography scan showing migrated foreign body (arrow) adjacent to right carotid sheath at level of hyoid bone.

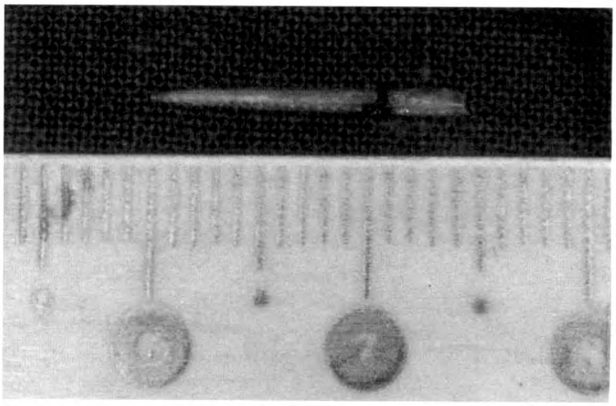


Fig 5. Typical migrating fish bone: sharp and linear.

Foreign Bodies. All the migrated foreign bodies were found to be linear, sharp-ended fish bones ranging in size from 0.7 to 3 cm (Fig 5). Most (16) of them were intramural, and among the 8 that were found extraluminally, 6 had a horizontal orientation. The other 18 bones had a vertical or oblique orientation.

Rigid Esophagoscopy. All patients with a history of ingested foreign body and a positive lateral neck radiograph had rigid esophagoscopy done under general anesthesia. No foreign bodies were found by this means. Nine esophagoscopies yielded normal findings, and 15 showed mucosal laceration, ulcers, or edema.

A foreign body is assumed to have migrated in the event of a positive lateral neck radiograph and a negative endoscopy, and a CT scan is subsequently done for further evaluation.

Neck Exploration. All 24 migrated foreign bodies had neck exploration done and the foreign body was found in 22 cases. Esophagostomy was performed in 12 cases. There was 1 complication, a recurrent laryngeal nerve palsy.

Of the 2 cases of failed neck exploration, 1 pa-

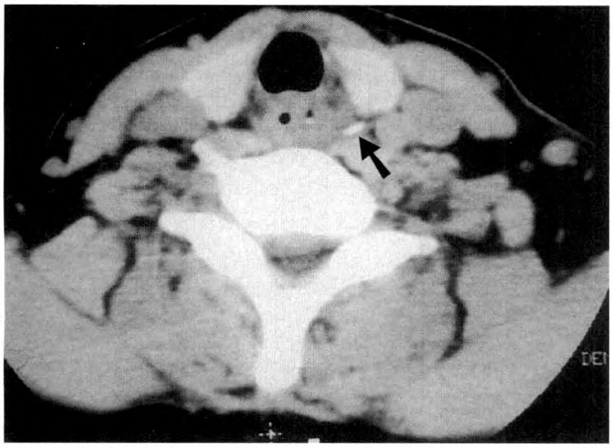


Fig 6. Axial computed tomography scan showing migrated foreign body (arrow) medial to left internal carotid artery and behind left lobe of thyroid.

tient had the foreign body embedded in prevertebral tissue at C-3, while the other had the foreign body in the posterior wall of the esophagus at C-6 (and no esophagostomy was done). Postoperative CT scans revealed absence of foreign bodies, and they were assumed to have been removed inadvertently during suction or exploration. All the patients had an uneventful recovery, with an average hospital stay of 5 days.

DISCUSSION

Exploring for a migrated foreign body has been described by some otolaryngologists to be like looking for a needle in a haystack. Because of the potential consequences, this can indeed be a therapeutic dilemma. A literature search has revealed only a few anecdotal case reports,[2,5] and this review of our series is an attempt to define our clinical protocol and examine the surgical technique in neck exploration for the successful management of migrated foreign bodies.

The clinical data showed that migrated foreign bodies can occur in any adult age group with no sexual predilection. It is interesting that in all these years of removing impacted fish bones from children, we did not find a single child with a migrated foreign body. The racial predisposition is reflective of the local Chinese habit of eating fish that is not filleted and using the mouth to separate the bones from the meat. The use of chopsticks and edentulous patients were found to be predisposing factors, as suggested also by Lim et al.[3] Contrary to prevailing opinion in Singapore, the duration of ingestion is no indicator of migration. Of our series, 75% presented with less than 24 hours of foreign body ingestion. Being unaware of this may result in a delay of diagnosis with potential grave consequences. All the migrated foreign bodies were sharp, linear fish bones rather than other shapes, ie, T-shaped fish bones, which are more likely to be impacted in the esophagus. The manner and forcefulness of swallowing[6] and the shape of the foreign body may be the primary causes of migration. Horizontal orientation of the fish bone, previously thought to be important,[5] was found in only 6 patients. However, horizontally oriented bones are more likely to migrate extraluminally in the path of least resistance. Symptoms of ipsilateral neck pain and dysphagia were predominant, while laryngeal rub and water drinking tests were often not diagnostic, again in contradistinction to impacted foreign bodies.[3]

Lateral neck radiographs were useful for documenting the presence of an esophageal foreign body, but could not determine whether migration had occurred. Rigid esophagoscopy that is negative for bones but shows signs of ulcer, laceration, or edema can often suggest the possibility of migration. Migration is assumed to have occurred in the presence of a documented foreign body on radiography with a negative endoscopy. A CT scan of the neck is the investigation of choice to confirm this in all these patients.

A CT scan is the primary tool of investigation because it can tell us the size, type, location, and orientation of the foreign body and, more importantly, the relationship of the foreign body to other vital structures such as the carotid sheath, hyoid bone, cricoid cartilage, and thyroid gland. Often, these structures serve as useful landmarks in a successful neck exploration. For example, the CT scan in Fig 6 showed the foreign body just medial to the internal carotid artery and behind the thyroid lobe at the level of the hyoid bone.

Neck Exploration Technique. The patient is under general anesthesia and placed supine with the neck extended by a sandbag beneath the shoulder blades. The incision is made in the ipsilateral side of the neck, usually at the hyoid bone and the anterior border of the sternomastoid muscle.

In our experience, the position of the foreign body in relation to the cervical vertebrae is not a useful landmark, because the surgical approach is from the front and the position of the foreign body may be altered with the position of the head and neck during surgery.

The tracheoesophageal groove is approached at the level at which the foreign body is related to fixed cartilaginous structures such as the hyoid bone or thyroid cartilage.

The recurrent laryngeal nerve in the groove is identified first before further exploration. The only case of nerve palsy occurred precisely because the nerve was not identified. The esophagus is then rolled between the fingers to feel for the approximate position of the foreign body, and often, incising the muscle layer of the esophagus (esophagostomy) without breaching the mucosa is necessary for finding and removing the foreign body. Loupes and microscopes are useful adjuncts to exploration, and meticulous hemostasis is essential. Repair is done in a single layer with 3-0 Vicryl sutures.

CONCLUSIONS

Although migrated foreign bodies are uncommon, review of our data has enabled us to define our protocol and the following conclusions.

1. The duration since ingestion and the symptoms of an impacted foreign body in general do not correlate well to suggest the presence of a migrated foreign body. A high index of suspicion is needed.
2. Migration is only suspected in the event of a positive lateral neck radiograph and a negative rigid esophagoscopy. Usually, a repeat endoscopy is performed to confirm a negative esophagoscopy.
3. A CT scan using 3-mm axial cuts and soft tissue windows is the investigation of choice in suspected migration of a foreign body.
4. All our migrated foreign bodies were linear, sharp-ended fish bones in adults. Most are likely to be intramural. Extraluminal migration is associated with horizontally oriented fish bones.
5. Whenever possible, cartilaginous landmarks such as the cricoid cartilage, thyroid bone, and thyroid cartilage and vital structures such as the carotid sheath are carefully noted in relation to the foreign body on CT scan.
6. Surgery is performed as a "planned emergency" during the day, with experienced supporting personnel, unless the patient is critically ill.
7. Meticulous surgical technique, as discussed, is critical to a successful outcome. Esophagostomy is necessary to remove intramural foreign bodies and does not increase morbidity.

REFERENCES

1. Leong HK, Chan R. Foreign bodies in the upper digestive tract. Singapore Med J 1987;28:162-5.

2. Muhanna AA, Abu-Chra KA, Dashti H, Behbehani A, Al-Naqeeb N. Thyroid lobectomy for removal of a fishbone. J Laryngol Otol 1990;104:511-2.

3. Lim CT, Quah R, Loh LE. A prospective study of ingested foreign bodies in Singapore. Arch Otolaryngol Head Neck Surg 1994;120:96-101.

4. Braverman I, Gomori JM, Polv O, Saah D. The role of CT imaging in the evaluation of cervical esophageal foreign bodies. J Otolaryngol 1993;22:311-4.

5. Sethi DS, Stanley R. Migrating foreign bodies in the upper digestive tract. Ann Acad Med Singapore 1992;21:390-3.

6. Dodds WJ, Stewart EJ, Logemann JA. Physiology and radiology of the normal oral and pharyngeal phases of swallowing. AJR Am J Roentgenol 1990;154:953-63.

Ann Otol Rhinol Laryngol 108:1999

ASTROCYTE REACTION IN THE RAT VESTIBULAR NUCLEI AFTER UNILATERAL REMOVAL OF SCARPA'S GANGLION

HONGYAN LI, MD, PHD
DONALD A. GODFREY, PHD
ALLAN M. RUBIN, MD, PHD
TOLEDO, OHIO

Unilateral vestibular ganglionectomy (UVG) results in a complete degeneration of vestibular nerve fibers and terminals in the ipsilateral vestibular nuclear complex (VNC). A subsequent glial reaction may affect the activities of VNC neurons and thereby influence compensation for lesion-induced vestibular disorders. Expression of glial fibrillary acidic protein (GFAP), a specific marker for reactive astrocytes, was demonstrated immunohistochemically in the rat VNC at 7, 14, and 35 days after UVG. An increased GFAP-positive astrocytic response was evident at 7 days after lesion in all the VNC regions on the lesioned side and in some regions on the unlesioned side and remained through 35 days. The glial response included hypertrophy, which was more prominent at 7 days than at 14 days or 35 days, and proliferation, more prominent at the later times, of GFAP-positive astrocytes. Astrocytic projections around VNC neuron somata and proximal dendrites increased in number and became thicker and more elongated, especially at 14 days, in the lateral vestibular nucleus. It is suggested that UVG results in a bilateral astrocytic reaction in the VNC that would affect the subsequent compensation.

KEY WORDS — glial fibrillary acidic protein, reactive astrocytosis, vestibular compensation, vestibular deafferentation, vestibular ganglionectomy.

INTRODUCTION

Since glial reactions, including proliferation and phagocytosis of decomposed nervous tissue, are associated with lesions,[1,2] they should occur along with vestibular nerve degeneration in the vestibular nuclear complex (VNC) following removal of Scarpa's ganglion.[3] Astrocytes, the major glial type involved in lesion-induced glial reactions in the central nervous system, can be identified by their increased expression of glial fibrillary acidic protein (GFAP)[4-8]; GFAP is the major protein constituent of glial intermediate filaments in differentiated fibrous and protoplasmic astrocytes.[5,9,10] Reactive formation of astroglia may affect some aspects of vestibular compensation after unilateral deafferentation, as it may influence the synaptic efficacy in the cochlear nucleus after cochlea removal,[11,12] through such mechanisms as space occupation or effects on neuronal nutrition or neurotransmitter availability. Increases of GFAP-positive astrocytes have been reported in the vestibular nerve root and the lateral vestibular nucleus (LVN) of the cat after vestibular neurectomy or labyrinthectomy.[13] However, there was no description of other VNC regions besides the LVN. The current study was carried out to provide detailed information about astrocytic reactions in all major VNC regions of the rat at several survival times after unilateral peripheral deafferentation. The information derived is important for our study on the mechanisms of lesion-induced vestibular compensation.

MATERIALS AND METHODS

Animals and Surgery. Thirteen adult male albino rats (Sprague-Dawley, 250 to 350 g) were equally divided into 1 control group and 3 lesion groups. After a dose of chloral hydrate (400 mg/kg, intraperitoneally), all 9 rats in the lesion groups were operated upon to remove Scarpa's ganglion on the left side by means of a previously reported surgical procedure.[3] After surgery, these animals were allowed to survive for 7, 14, or 35 days. During the survival period, each rat was given a daily intramuscular dose of Liquamycin LA-200 (20 mg/kg, Pfizer) for 3 days. Also, each was given a subcutaneous injection of 10 to 15 mL of 5% dextrose daily for up to 7 days to prevent dehydration that could result from the impaired ability to maintain equilibrium. Tests for vestibular disorders were carried out each day with the criteria described previously.[3] No surgery was done on the 4 control rats. One control rat was treated with the same medications (anesthetic, antibiotic, and dextrose) as the lesioned rats and was painlessly sacri-

---

From the Department of Otolaryngology–Head and Neck Surgery, The Medical College of Ohio, Toledo, Ohio. This study was supported by National Institutes of Health grant R01-DC02550 and intramural funds from the Department of Otolaryngology–Head and Neck Surgery, Medical College of Ohio. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Medical College of Ohio.

CORRESPONDENCE — Hongyan Li, MD, PhD, Dept of Otolaryngology–Head and Neck Surgery, The Medical College of Ohio, 3065 Arlington Ave, Toledo, OH 43614.

ficed at 14 days after anesthesia. All the procedures related to the use of animals in this study were approved by the Medical College of Ohio Institutional Animal Care and Use Committee.

Tissue Preparation. Upon the date of sacrifice, rats were deeply anesthetized with sodium pentobarbital (approximately 65 mg/kg, intraperitoneally) and intracardially perfused with 0.1 mol/L phosphate buffer, pH 7.40 (PB), containing 0.9% sodium chloride (PBS), followed by 4% paraformaldehyde in 0.1 mol/L PB and 5% sucrose in 0.1 mol/L PB. The brains were removed and post-fixed in the same fixative for 1 hour and then in 30% sucrose for up to 48 hours at 4°C. Brain sections (20 or 50 μm) were cut at –20°C and collected in 0.1 mol/L PBS (4°C). Sections were then preincubated in 0.1 mol/L PBS containing 10% normal goat serum and 0.3% Triton X-100 for 1 hour at room temperature, rinsed, and incubated at 4°C overnight with 1:100 rabbit anti human GFAP antibody (Chemicon International, Inc) in 0.1 mol/L PBS containing 1% normal goat serum, 0.3% Triton X-100, and 0.03% sodium azide. After incubation, sections were rinsed in 0.1 mol/L PBS and incubated with biotinylated goat antibody to rabbit IgG and then with avidin-peroxidase complex (Vectastain ABC systems, Novocastra Laboratories Ltd). After washing, these sections were stained in 50 mL of 0.1 mol/L PB containing 25 mg of 3,3'-diaminobenzidine and 12.5 μL of hydrogen peroxide. Controls included simultaneous staining of sections incubated in solutions containing no primary antibody or normal rabbit serum as a substitute for specific primary antibody. In either treatment, no specific staining was observed. In some animals, adjacent sections were Nissl-stained. Stained sections were observed and photographed under a Leitz microscope.

Morphologic Measurements and Analysis. To quantify the differences of GFAP immunoreactivity between lesioned and unlesioned sides for all the VNC regions, stained sections were scanned under a Leitz Orthoplan microscope (1.63× objective lens) with a video camera, and the images were analyzed for the averaged optical density of each VNC region by a computerized imaging system (NeuroLucida 2.1). To optimize the accuracy of these measurements, the system was calibrated with a Kodak photographic step tablet (No. 2, calibrated, Cat. 152 3406) for each section so that all the readings were in the linear range. To avoid errors due to possible variations in section thickness, the optical densities measured from the inferior cerebellar peduncle were used to normalize the measurements from all the VNC regions on both sides of each section. The significances of bilateral differences were analyzed with a paired *t*-test for each VNC region at each survival time. The variances of such bilateral differences across different survival times were checked by analysis of variance followed by the Tukey test. Differences or variances were considered significant if $p \leq .05$.

RESULTS

Surgical Lesions. Complete removal of Scarpa's ganglion was confirmed in all the lesioned rats by checking the operated temporal bones, the transected central portions of the vestibular nerve roots during brain removal, and the stained sections. In 2 rats 7 days after lesion, direct damage was found in the ventral cochlear nucleus near Scarpa's ganglion on the lesioned side. However, there was no damage to any other area or at any other time.

GFAP Immunoreactivity in VNC of Control Rats. In control rats, GFAP-positive astrocytes were observed in all the VNC regions (Fig 1A). Morphologic characteristics of these astrocytes suggested that they were mainly of the protoplasmic type (Fig 2Aa,b). The GFAP-positive astrocytes in the medial vestibular nucleus (MVN; Fig 2Aa) were relatively smaller than those in the LVN (Fig 2Ab), with fewer and shorter processes. In both the rostral and caudal parts of the MVN, more labeled astrocytes were found in the dorsal region, especially in the area below the fourth ventricle and near the prepositus hypoglossal nucleus and reticular formation, than in the central region. In the middle part of the MVN, however, such variations were not obvious. In the spinal vestibular nucleus (SpVN) and LVN, labeled astrocytes were sparsely distributed, they had elongated projections, and each occupied more space than those in the MVN. The GFAP-positive astrocytes in the SpVN had their somata and processes in narrow spaces between and oriented parallel to longitudinally passing fiber bundles, but were never found inside the bundles. Compared to those in the SpVN, the GFAP-positive astrocytes in the LVN were more diversely oriented; they contacted most Deiters' cell bodies with their processes (Fig 2Ab). In the superior vestibular nucleus (SuVN), GFAP-positive astrocytes resembled those found in the MVN, except that they were relatively smaller and fewer. There were a few GFAP-positive astrocytes in the post-ganglionic vestibular nerve root. These cells had spindle-shaped somata and long processes paralleling vestibular nerve fibers. The GFAP immunohistochemistry in the control rat treated with the same medications as the lesioned rats showed the same results as in the untreated control rats.

GFAP Immunoreactivity in VNC of Rats After

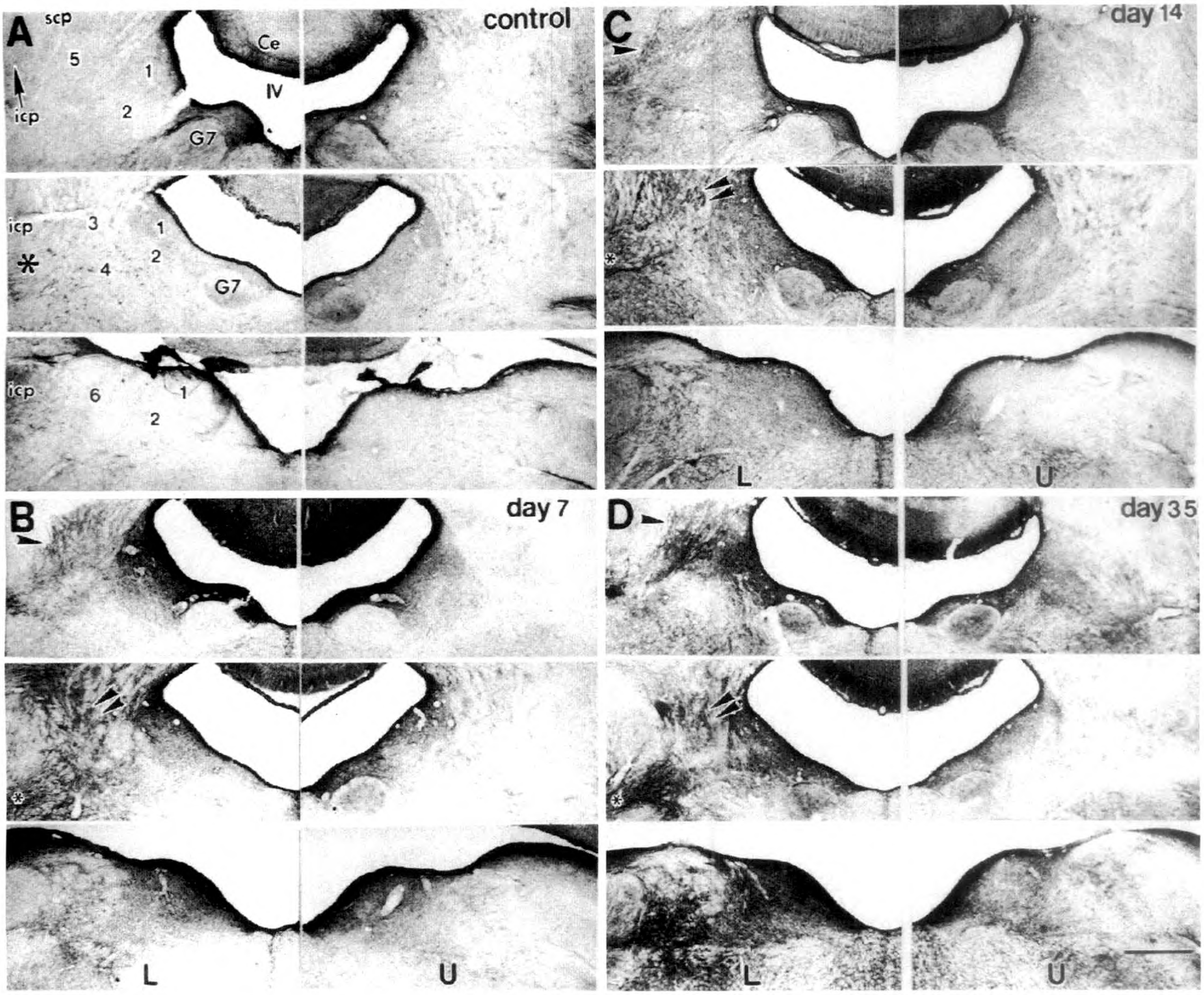


Fig 1. Glial fibrillary acid protein (GFAP) immunoreactivity in vestibular nuclear complex in A) control and B-D) unilaterally vestibular ganglionectomized rats. Three sections, from most rostral at top to most caudal at bottom, are shown for each side for 1 rat of each group. Entry zone of vestibular nerve root of control rat is indicated by large asterisk in A. In B-D, increased GFAP immunoreactivity in entry zone of vestibular nerve root is indicated by small asterisk, in dorsal part of lateral vestibular nucleus by double arrowheads, and in dorsolateral part of superior vestibular nucleus by single arrowhead. 1 — dorsal part of medial vestibular nucleus; 2 — ventral part of medial vestibular nucleus; 3 — dorsal part of lateral vestibular nucleus; 4 — ventral part of lateral vestibular nucleus; 5 — superior vestibular nucleus; 6 — spinal vestibular nucleus; Ce — cerebellar cortex; G7 — genu of facial nerve; icp — inferior cerebellar peduncle; IV — fourth ventricle; L — lesioned side; scp — superior cerebellar peduncle; U — unlesioned side; scale bar — 1 mm.

UVG. After unilateral vestibular ganglionectomy (UVG), increases in GFAP immunoreactivity were found bilaterally in the VNC, but were more obvious on the lesioned side (Fig 1B-D). As in control rats, labeled astrocytes appeared to be mainly of the protoplasmic type. The more notable changes at each survival time are described below.

At 7 days after UVG, glial reaction was evident in all the VNC regions on the lesioned side, most obviously in the entry zone of vestibular nerve fibers, located in the ventrolateral portion of the VNC (Fig 1B). Compared to the unlesioned side, GFAP-positive immunoreactivity was significantly higher in all the VNC regions, except the dorsal part of the MVN, on the lesioned side (Fig 3). The reaction on the unlesioned side was mostly limited to the dorsal parts of both the MVN and LVN (Fig 1B). The glial responses in the vestibular nerve root consisted of thick, coarse, and heavily stained bundles formed by astrocytic projections, coursing between the inferior cerebellar peduncle and the spinal trigeminal tract and extending from the transected edge to the entry zone of the VNC. Under high magnification, this glial response appeared as significant astrocytic hypertrophy and moderate proliferation (Fig 2Ba-c). In the LVN on the lesioned side, especially its ventral part, GFAP-positive astrocytes showed obvious hypertrophy and proliferation (Fig 2Bb). Neurons in both the ventral and dorsal parts of the LVN

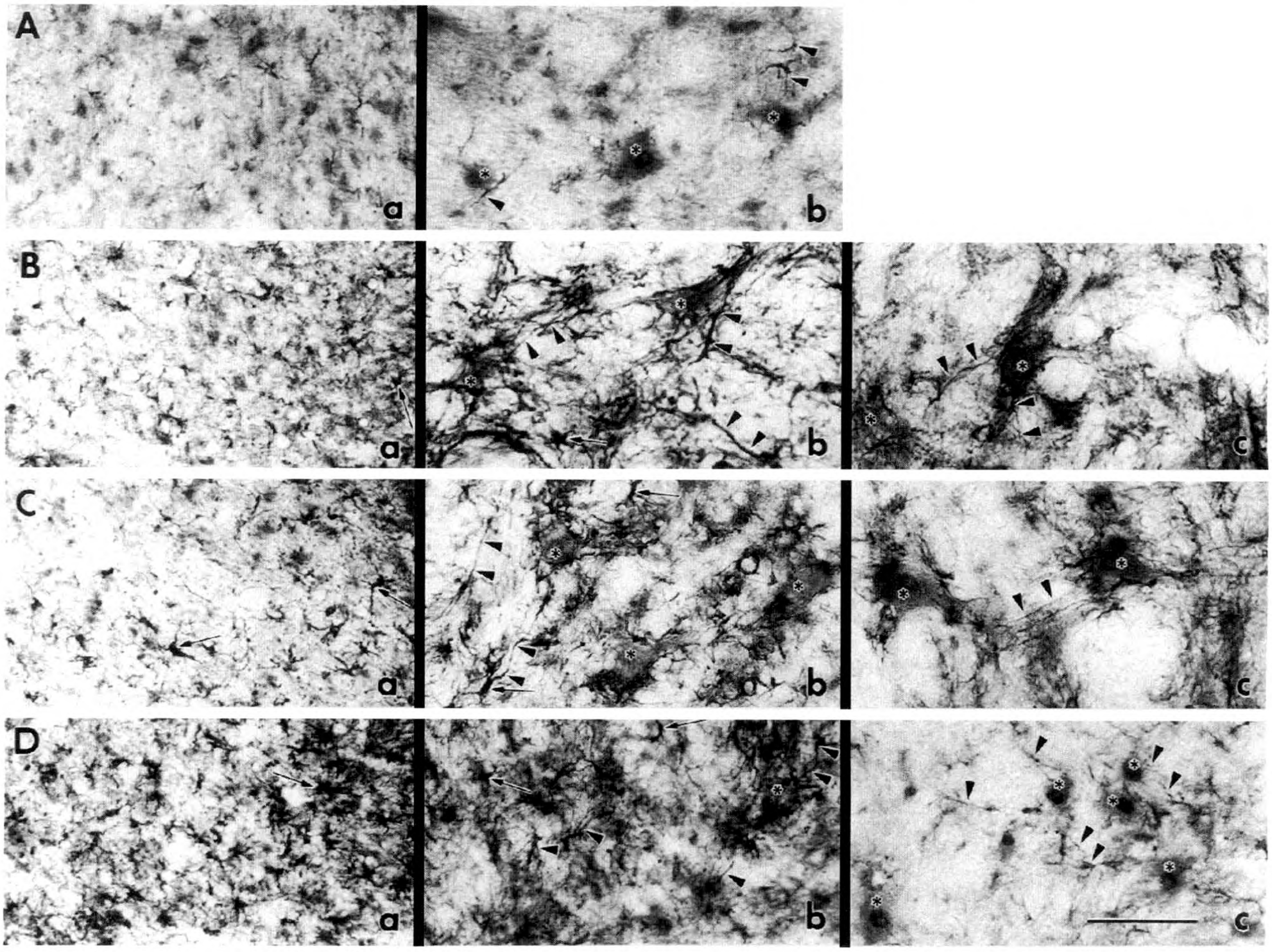


Fig 2. Higher magnification of GFAP immunoreactivity in medial and lateral vestibular nuclei. Pictures from 1 animal of each group are arranged in rows. A) Control. B) Seven days after unilateral vestibular ganglionectomy. C) Fourteen days after same. D) Thirty-five days after same. Pictures labeled with a are from corresponding regions in medial vestibular nucleus on left side (operated side for lesioned animals). Those labeled b are from corresponding regions in lateral vestibular nucleus on left side (operated side for lesioned animals). Pictures labeled with c are from unlesioned-side lateral vestibular nucleus (see Fig 1A for identification of these regions). Asterisks — lateral vestibular nucleus neuron cell bodies; arrows — astrocyte cell bodies; arrowheads — astrocytic projections; scale bar — 0.1 mm.

were surrounded by thick and elongated GFAP-positive astrocytic projections. A similar pattern, but with somewhat less dense glial response, was also identified in the LVN on the unlesioned side, mainly in its dorsal part (Fig 2Bc). In the MVN, significant hypertrophy and proliferation of GFAP-positive astrocytes were both evident (Fig 2Ba). The hypertrophy of GFAP-positive astrocytes in the MVN was different in several ways from that in the LVN. First, labeled astrocytes in the MVN showed significantly enlarged somata, more obvious than in the LVN. Second, the labeled astrocytic projections in the MVN were short and thin, and in each process the GFAP immunoreactivity was identified mainly in the proximal part. In contrast, the labeled processes in the LVN were long and thick, with dense GFAP immunoreactivity found throughout their lengths. Third, the tangles of labeled astrocytic processes around the LVN neurons were not clearly identified in the MVN. The pattern of astrocytic reactions in the SuVN was more like that in the MVN, while that in the SpVN resembled that in the LVN. Within the SuVN, one of the recognized differences from the control was an obvious astrocytic reaction in a band immediately medial to the inferior cerebellar peduncle and ventral to the superior cerebellar peduncle (Fig 1B). High magnification revealed slightly larger and more numerous GFAP-positive astrocytes in this region than in the rest of the SuVN, without any other clear difference. Of interest, as in the LVN, a similar reaction was found in the corresponding contralateral region (Fig 1B).

At 14 days after lesion, compared to 7 days, hypertrophy of GFAP-positive astrocytes became somewhat less obvious, whereas the numbers of GFAP-positive astrocytes further increased (Fig 2Ca-c). Labeled astrocytes in the MVN appeared to have small-

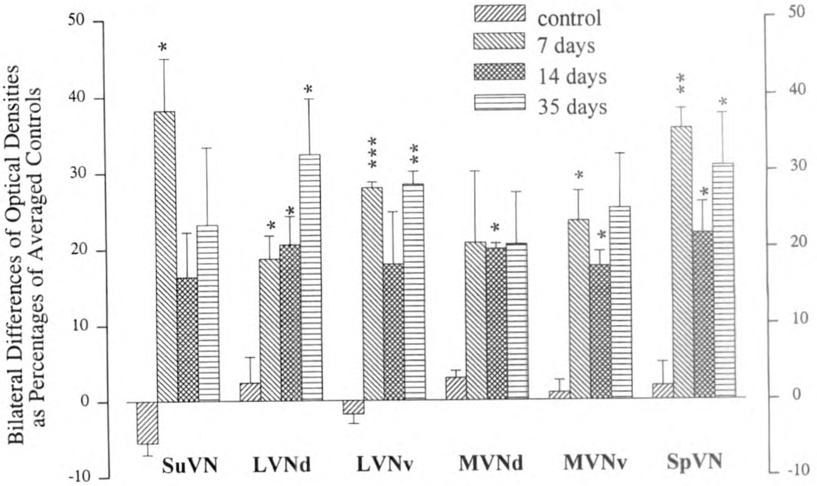


Fig 3. Bilateral differences in density of GFAP-positive immunoreactivity in regions before and after unilateral vestibular ganglionectomy. Data are presented as percentages of averaged optical density measured from both sides of 3 control animals. Asterisks represent results of paired *t*-tests for bilateral differences: single asterisk — $p < .05$; double asterisk — $p < .01$; triple asterisk — $p < .001$. SuVN — superior vestibular nucleus; LVNd — dorsal part of lateral vestibular nucleus; LVNv — ventral part of lateral vestibular nucleus; MVNd — dorsal part of medial vestibular nucleus; MVNv — ventral part of medial vestibular nucleus; SpVN — spinal vestibular nucleus.

er somata than at 7 days, while their processes appeared more elongated (Fig 2Ca). In contrast, GFAP-positive astrocytic processes at 14 days appeared thinner and more weakly labeled in the LVN, except at their terminal portions, which were closely associated with the LVN neuronal cell bodies (Fig 2Cb,c). A similar pattern of astrocytic reaction was observed in both the lesioned- and unlesioned-side VNCs, although it was more obvious on the lesioned side (Fig 2Cb,c). The overall density of GFAP immunoreactivity was still significantly higher on the lesioned side than the unlesioned side for most VNC regions (Fig 3). As noted at 7 days, astrocytic reaction was obvious in both the dorsal and ventral parts of the LVN on the lesioned side, but only in the dorsal part on the unlesioned side. In the SpVN, changes were similar to those in the LVN. The astrocytic changes in the SuVN were more obvious than those at 7 days, but with similar patterns.

The astrocytic reaction remained significant in all the VNC regions at 35 days after lesion (Fig 1D), and the bilateral difference of GFAP immunoreactivity remained significant in the dorsal and ventral parts of the LVN, and in the SpVN (Fig 3). Compared to the situation at 14 days, several changes at this survival time were recognized. First, the sizes of GFAP-positive astrocyte somata were further reduced, although still larger than in the control animals (Fig 2Da-c). Second, there was a further increase in number of labeled astrocytes, especially in the MVN (Fig 2Da) and SuVN. Third, there was significant shrinkage in the sizes of the terminal portions of GFAP-positive astrocytic processes around LVN neurons, although there was no obvious change in their density. More labeled processes tended to approach and contact LVN neurons perpendicularly than at 14 days (Fig 2Db,c). Fourth, the bilateral increase in astrocytic reaction in the region of the SuVN adjacent to the inferior and superior cerebellar peduncles became more obvious than at 14 days (Fig 1D).

DISCUSSION

Astrocytes in VNC of Control Rats. Astrocytes are the most numerous glial cells in the central nervous system, and their function is important for many aspects of the normal function of VNC neurons. Consistent with previous reports that suggest that protoplasmic astrocytes are the major astrocytes in gray matter[14] and that the protoplasmic astrocytes are preferentially labeled when paraformaldehyde is used as fixative for GFAP immunohistochemistry,[15] the GFAP-positive astrocytes in the VNC, both in control and lesioned rats, appeared to be mainly of the protoplasmic type. The variations in astrocyte morphology and distribution among the different VNC regions may reflect their adaptations to different environments.[2] In the LVN, where neurons are large and sparsely distributed among axonal bundles, so also are the astrocytes. These astrocytes, with their long and thin processes oriented within the limited space between neurons and fiber bundles, can make efficient contacts with the neurons. In the MVN, where neurons are smaller but more densely populated and where axonal bundles are sparse, the astrocytes are smaller and more densely distributed. Their shorter processes should be sufficient in view of their dense distribution. The astrocyte morphologies and distributions in the SpVN and SuVN likewise parallel the neuron characteristics: those in the SpVN somewhat resemble those in the LVN, whereas those in the SuVN resemble those in the MVN.

Astrocytic Reaction to UVG in VNC. The elevated astrocytic reaction in the VNC regions after UVG and the resulting complete degeneration of vestibular nerve fibers and terminals[3] may reflect several processes. These may include removal of degeneration products, proliferation to fill the space left by the degeneration of vestibular nerve fibers and terminals, and alterations of activity to accommodate changes of VNC neuron activities.

The timing of changes in the morphology of astrocytes in the VNC after UVG suggested that the astrocytic response to vestibular nerve degeneration was characterized mainly by hypertrophy during the first 2 postoperative weeks and mainly by proliferation thereafter. The early changes in astrocytes might aid the VNC neurons in surviving the sudden loss of synaptic activation, as well as possible cytotoxicity of glutamate released from degenerating vestibular nerve fibers.[16-19] The later changes would be aimed at rebuilding the local environment to facilitate the plasticity in the VNC neuron activities[20,21] and patterns of local synaptic connections.[22-25] In addition, the evolution of the pattern of astrocytic processes near VNC neurons to more intimate contacts at the later times, especially in the LVN, suggests increased efficiency of astrocytic influence on VNC neurons.

The increased astrocytic reaction was more evident in the VNC regions on the lesioned side than on the unlesioned side. Although evident visually, increased densities of astrocytic labeling could not be quantified and compared statistically across animals because of significant variations in the density of GFAP immunoreactivity among animals.

An interesting finding in this study was the bilaterally increased astrocytic reaction in some VNC regions, ie, the dorsal part of the LVN, the dorsal part of the MVN, and the part of the SuVN adjacent to the inferior and superior cerebellar peduncles. Cass and Goshgarian[13] reported such a change in the dorsal part of the LVN of the cat after vestibular neurectomy and attributed it to indirect mechanisms secondary to changes in LVN neuron activities during vestibular compensation. Since there is no primary vestibular projection to the contralateral VNC, the activity changes of the VNC neurons on the side opposite to deafferentation were considered to result from changes in activity of other inputs, such as cerebellar projections.[13] Our observations in rats support this hypothesis, since the increased astrocytic reaction in the contralateral VNC was least obvious in the SpVN, for which there is least evidence of either cerebellar or commissural connections.[26,27] The change in the SuVN further correlates with findings of significant loss of synaptic profiles and signs of atrophy of SuVN vestibulo-ocular neurons in cats at long times after contralateral vestibular neurectomy.[23] The increased astrocytic reaction on the unlesioned side did not likely result from transneuronal degeneration, since previous studies suggested that peripheral vestibular deafferentation did not cause significant loss of commissural neurons on the lesioned side.[25,28] A recent study suggests that at a longer survival time after unilateral vestibular neurectomy, degeneration of contralateral vestibular nerve synaptic terminals may contribute to the progressive loss of synaptic profiles in VNC regions on the unlesioned side.[24] However, it is not clear whether the increased GFAP immunoreactivity in the contralateral SuVN in our study was related to such a loss, since there is no evidence for such degeneration within 35 days.

The reported absence of glial reaction in the VNC on the unlesioned side after unilateral labyrinthectomy, as evaluated mainly by immunohistochemistry for vimentin,[29] might imply a less than complete vestibular deafferentation, especially since such a bilateral effect was reported previously following unilateral labyrinthectomy, by means of immunohistochemistry for GFAP.[13] Although labyrinthectomy may induce a weaker glial response in the VNC regions than does vestibular ganglionectomy,[13] because of the limited amount of vestibular nerve degeneration,[3,29] effects on the VNC regions contralateral to the lesion would be functional with both lesions, since there was no degeneration on the contralateral side in either case.[3,29] Alternatively, other factors, such as species differences, might be involved.

The astrocytic reaction in the VNC may significantly affect some aspects of vestibular compensation. While astrocytes can facilitate the maintenance of VNC neuron metabolism through mechanisms such as transporting nutrients and waste products between neurons and blood and regulating glutamate and potassium concentration in the synaptic spaces, they may also have negative effects. For example, the astrogliosis between the VNC neurons may act as a physical barrier against the remodeling of local VNC neuron circuits through such mechanisms as axonal sprouting. Previous studies have revealed that the expression of GFAP by astrocytes can be modulated by cytokines and neurotrophins[30] and that astrocytes can produce many chemicals, including neuropeptides, neurotransmitters, and growth factors, once thought to be produced only by neurons.[31] Further studies on the roles of astrocytes in the deafferented VNC may provide important information relevant to our understanding of vestibular compensation.

The astrocytic reaction may be only part of the glial response in the VNC to the degeneration of vestibular nerve terminals. Other glia, such as microglia and oligodendrocytes, may also influence vestibular compensation. Among the glia, microglia are the most rapidly responsive to axonal degeneration and are responsible for removing degenerated debris before repairs take place.[1] Activated microglia also trigger astrocytic reactions by secreting cytokines.[32] Oligodendrocytes are important for myelin formation.[33] So far, there is no clear understanding about the behaviors of these two glial types in the deafferented VNC during vestibular compensation.

In summary, UVG induced significant astrocytic reaction in all the VNC regions on the lesioned side and in some regions on the unlesioned side. The astrocytic reaction was dominated by hypertrophy during the first 1 to 2 survival weeks and then by proliferation. The increased GFAP immunoreactivity in the contralateral VNC suggests an indirect response and may involve cerebellar and/or commissural projections. Although the astrocytic response may protect the VNC neurons from the toxicity of extracellular glutamate and support the modulation of VNC neuron activities, it may also reduce the efficiency of vestibular compensation by preventing formation of new connections to the deafferented VNC neurons.

ACKNOWLEDGMENTS — The authors thank Wei Kong and Timothy G. Godfrey for their assistance during this study and Edward Calomini for his help in photograph preparation.

REFERENCES

1. Streit WJ, Graeber MB, Kreutzberg GW. Functional plasticity of microglia: a review. Glia 1988;1:301-7.

2. Hatten ME, Liem RHK, Shelanski ML, Mason CA. Astroglia in CNS injury. Glia 1991;4:233-43.

3. Li H, Godfrey DA, Rubin AM. Comparison of surgeries for removal of primary vestibular inputs: a combined anatomical and behavioral study in rats. Laryngoscope 1995;105:417-24.

4. Bignami A, Dahl D. Specificity of the glial fibrillary acidic protein for astroglia. J Histochem Cytochem 1977;25:466-9.

5. Choi BH. Glial fibrillary acidic protein in radial glia of early human cerebrum: a light and electron microscopic immunoperoxidase study. J Neuropathol Exp Neurol 1986;45:408-18.

6. Noppe M, Crols R, Andries D, Lowenthal A. Determination in human cerebrospinal fluid of glial fibrillary acidic protein, S-100 myelin basic protein as indices of non-specific or specific central nervous tissue pathology. Clin Chim Acta 1986; 155:143-50.

7. Roessmann U, Gambetti P. Pathological reaction of astrocytes in perinatal brain injury. Immunohistochemical study. Acta Neuropathol (Berl) 1986;70:302-7.

8. Scotti AL, Monard D, Nitsch C. Re-expression of glial-derived nexin/protease nexin 1 depends on mode of lesion-induction or terminal degeneration: observations after excitotoxin or 6-hydroxydopamine lesions of rat substantia nigra. J Neurosci Res 1994;37:155-68.

9. Eng LF. The glial fibrillary acidic (GFA) protein. In: Bradshaw RA, Schneider DM, eds. Proteins of the nervous system. 2nd ed. New York, NY: Raven Press, 1980:85-117.

10. Eng LF. Glial fibrillary acidic protein (GFAP): the major protein of glial intermediate filaments in differentiated astrocytes. J Neuroimmunol 1985;8:203-14.

11. Canady KS, Rubel EW. Rapid and reversible astrocytic reaction to afferent activity blockade in chick cochlear nucleus. J Neurosci 1992;12:1001-9.

12. Rubel EW, MacDonald GH. Rapid growth of astrocytic processes in n. magnocellularis following cochlea removal. J Comp Neurol 1992;318:415-25.

13. Cass SP, Goshgarian HG. Increased glial fibrillary acidic protein immunoreactivity in astrocytes within the lateral vestibular nucleus of the cat following labyrinthectomy and vestibular neurectomy. Ann Otol Rhinol Laryngol 1990;99:221-7.

14. Ong WY, Garey LJ, Leong SK, Reynolds R. Localization of glial fibrillary acidic protein and glutamine synthetase in the human cerebral cortex and subcortical white matter. A double immunolabelling and electron microscopic study. J Neurocytol 1995;24:602-10.

15. Shehab SA, Cronly-Dillon JR, Nona SN, Stanfford CA. Preferential histochemical staining of protoplasmic and fibrous astrocytes in rat CNS with GFAP antibodies using different fixatives. Brain Res 1990;518:347-52.

16. Rothman S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. J Neurosci 1984;4:1884-91.

17. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic/ischemic brain damage. Ann Neurol 1986;19: 105-11.

18. Rothman SM, Thurston JH, Hauhart RE. Delayed neurotoxicity of excitatory amino acids in vitro. Neuroscience 1987; 22:471-80.

19. Baudry M, Thompson RF, Davis JL, eds. Synaptic plasticity: molecular, cellular, and functional aspects. Boston, Mass: Massachusetts Institute of Technology, 1993.

20. Dieringer N. "Vestibular compensation": neuroplasticity and its relations to functional recovery after labyrinthine lesions in frogs and other vertebrates. Prog Neurobiol 1995;46:97-129.

21. Smith PF, Curthoys IS. Mechanisms of recovery following unilateral labyrinthectomy: a review. Brain Res Brain Res Rev 1989;14:155-80.

22. Gacek RR, Lyon MJ, Schoonmaker JE. Morphologic correlates of vestibular compensation in the cat. Acta Otolaryngol Suppl (Stockh) 1989(suppl 462).

23. Gacek RR, Lyon MJ, Schoonmaker J. Ultrastructural changes in contralateral vestibulo-ocular neurons following vestibular neurectomy in the cat. Acta Otolaryngol Suppl (Stockh) 1991(suppl 477).

24. Gacek RR, Schoonmaker J, Lyon MJ. Ultrastructural changes in contralateral superior vestibulo-ocular neurons one year after vestibular neurectomy in the cat. Acta Otolaryngol Suppl (Stockh) 1992(suppl 495).

25. Guyot J-P, Lyon MJ, Gacek RR, Magnin C. Ultrastructural changes in superior vestibular commissural neurons following vestibular neurectomy in the cat. Ann Otol Rhinol Laryngol 1995;104:381-7.

26. Wilson VJ, Melvill Jones G. Labyrinthine input to the vestibular nuclei and reticular formation. In: Wilson VJ, Melvill

Jones G, eds. Mammalian vestibular physiology. New York, NY: Plenum Press, 1979:125-68.

27. Mehler WR, Rubertone JA. Anatomy of the vestibular nucleus complex. In: Paxinos G, ed. Hindbrain and spinal cord. Orlando, Fla: Academic Press, 1985:185-219. (The rat nervous system; vol 2.)

28. Galiana HL, Flohr H, Melvill Jones GA. A re-evaluation of intervestibular nuclear coupling: its role in vestibular compensation. J Neurophysiol 1984;51:242-59.

29. De Waele C, Campos Torres A, Josset P, Vidal PP. Evidence for reactive astrocytes in rat vestibular and cochlear nuclei following unilateral inner ear lesion. Eur J Neurosci 1996; 8:2006-18.

30. Laping NJ, Teter B, Nichols NR, Rozovsky I, Finch CE. Glial fibrillary acidic protein: regulation by hormones, cytokines, and growth factors. Brain Pathol 1994;4:259-75.

31. McMillian MK, Thai L, Hong JS, O'Callaghan JP. Brain injury in a dish: a model for reactive gliosis. Trends Neurosci 1994;17:138-42.

32. Schauwecker PE, Steward O. Genetic influences on cellular reactions to brain injury: activation of microglia in denervated neuropil in mice carrying a mutation (Wld^s) that causes delayed Wallerian degeneration. J Comp Neurol 1997;380:82-94.

33. Dubois-Dalcq M. Regeneration of oligodendrocytes and myelin. Trends Neurosci 1995;18:289-91.

≈

MENIERE'S DISEASE

The Fourth International Symposium on Meniere's Disease will be held in Paris, France, April 11-14, 1999. For information, contact Administrative and Scientific Secretariat, SOCFI/MENIERE '99, 14 rue Mandar, 75002 Paris, France; telephone 33 (0) 1 44 88 25 25; fax 33 (0) 1 40 26 04 44; e-mail fournier@socfi.fr.

Ann Otol Rhinol Laryngol 108:1999

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF BILATERAL CAROTID ARTERY OCCLUSION CAUSED BY NEAR-SUICIDAL HANGING

WOLFGANG MAIER, MD
FREIBURG, GERMANY
SHELTON MALATSKEY, MD
HAIFA, ISRAEL
MILO FRADIS, MD
HAIFA, ISRAEL
ANNETTE KREBS, MD
FREIBURG, GERMANY

In cases of attempted suicide by hanging, a combination of mechanisms causing local destruction of the pharynx, larynx, vessels, and spine, as well as neurologic complications, has to be considered. We present a case of hanging in which a deeply unconscious patient without any palpaple pulsation of the carotid arteries was referred to our otolaryngology department. Computed tomography and angiography showed parapharyngeal air, complete obstruction of both common carotid arteries, and a compensatory circulation through the vertebral arteries. Three hours after the trauma, surgical exploration with resection of the enrolled intima of both carotid arteries and repair of the pharynx was performed. The patient awoke with an infarct of the right hemisphere with incomplete left hemiparesis the next day, but symptoms slowly declined during the following months, and the patient learned swallowing again perfectly. We conclude from our experience that in near-hanged patients a prompt onset of adequate diagnostic and therapeutic measures is mandatory, as good neurologic and functional results may occur even in cases with coma and severe destruction of the carotid arteries and pharyngeal and laryngeal structures. Surgical repair of blunt carotid lesions is recommended and may be crucial for a good outcome.

KEY WORDS — blunt carotid trauma, brain circulation, carotid artery, hanging, neck trauma, suicide.

INTRODUCTION

Hanging is the most common form of achieving death by suicide in Europe, and it is the third most frequent way of attempting suicide, following drug overdose and wrist-slashing.[1-3] Almost half of suicides committed by men are by hanging.[1,2] In the United States, firearm-related suicides are most common (and more frequent than in Canada, with its more restrictive firearm regulations), and hanging is the second most common method in the United States, followed by poisoning.[4,5] From 1980 to 1992 in the United States, the proportion of suicide by hanging increased.[4]

Hanging can be classified as typical when the point of suspension is central over the occiput, and atypical when it is in any other position. In near-hanging cases, local injuries and neurologic complications do occur.[6] The force necessary to cause obstruction of the arteries and the air passage is usually obtained by hanging in the typical position only.[7] Hanging is considered to be complete if the whole body is suspended in the air, and incomplete if some part of the body touches the ground. We present a case of near-hanging in which vascular, pharyngolaryngeal, and neurologic injuries were sustained.

CASE REPORT

A 54-year-old man was admitted to the Freiburg University otolaryngology department after an attempted suicide by hanging. According to the relatives, the used rope broke, and the suicidal man fell and managed to crawl into the next room. The attending physician found the patient awake at first, but he rapidly became unconscious and had to be intubated. Then he was sent to the university hospital. On arrival, the patient was in a profound stuporous state. On his neck, there were circular marks made by the rope. The pulse could not be palpated over either carotid artery. Subcutaneous emphysema was found around the throat. A computed tomography (CT) scan of the brain showed no signs of intracerebral bleeding. Angiography of the carotid arteries revealed occlusion of both common carotid arteries in the middle third, just under the carotid bulb (Fig 1A). Although the internal carotid arteries were not visualized, both anterior and posterior cerebral arteries and the left middle cerebral artery filled through the vertebral and basilar arteries and the circle of Willis (Fig 1B). The right middle cerebral artery was not perfused. A

From the Department of Otorhinolaryngology, University Hospital, Freiburg, Germany (Maier, Krebs), and the Department of Otolaryngology, Bnai Zion Medical Center, Haifa, Israel (Fradis, Malatskey).

CORRESPONDENCE — Wolfgang Maier, MD, Dept of Otorhinolaryngology (HNO-Klinik), Universitätsklinik Freiburg, Killianstrasse 5, D-79106 Freiburg, Germany.

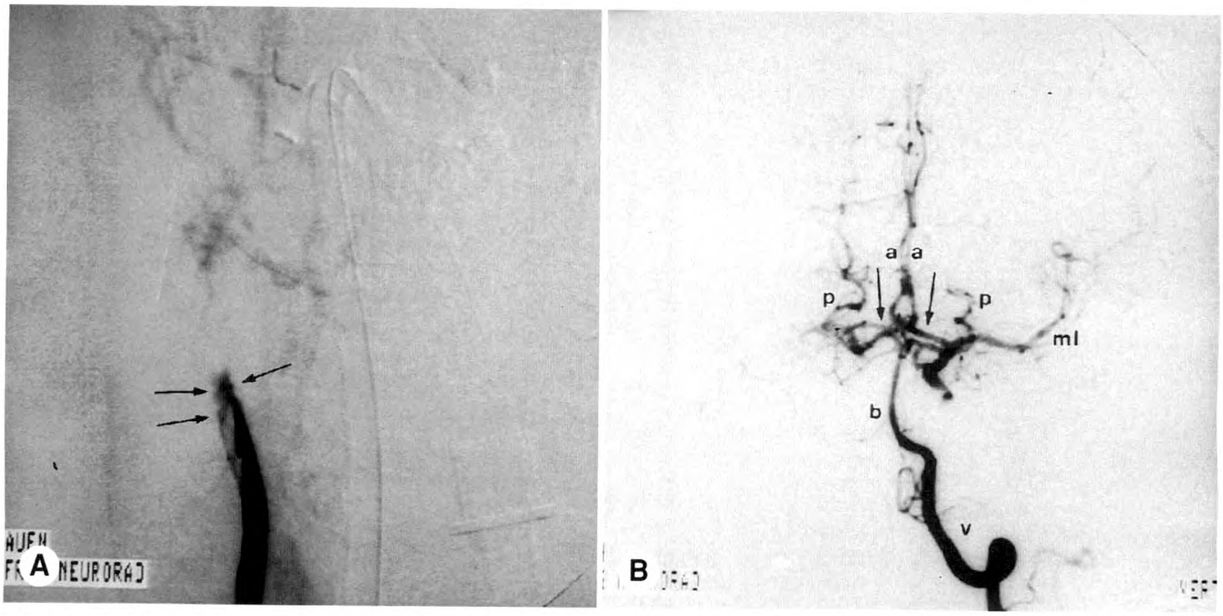


Fig 1. Angiography of head and neck arteries showed complete occlusion of both common carotid arteries. A) Right side shows contours of thrombus (arrows). On left side, dissection and occlusion were found, but no thrombus. These findings were confirmed intraoperatively. B) Anterior (a) and posterior (p) cerebral arteries and left middle (ml) cerebral artery filled well through vertebral (v) arteries, basilar (b) arteries, and circle of Willis (arrows). Right middle cerebral artery was not perfused in vertebral artery angiography.

CT scan of the neck showed a fracture of the hyoid bone without displacement, and a suspected fracture of the upper margin of the thyroid cartilage. Subcutaneous emphysema and air pockets were present in the parapharyngeal, retropharyngeal, and paralaryngeal areas.

The same night (3 hours after the attempted suicide), the patient underwent surgical exploration of the neck under general anesthesia. A vascular surgeon opened the carotid arteries by longitudinal incision after clamping the proximal and distal parts of the artery with vessel loops. On the right side, a thrombus was found and was extracted by a Fogarty catheter. Circulation was restored temporarily by insertion of an intraluminal shunt. A portion of the enrolled intima of the common carotid arteries was resected, and the intima was adapted to the arterial wall with U-shaped sutures. At the end of the operation, both carotid arteries were intact and had a good pulsation. In addition, a tear was found in the vallecula, between the epiglottis and the base of the tongue. The pharynx had been ruptured on both sides, between the lower poles of the tonsils and the pyriform sinuses, and only its posterior wall had intact mucosa. Both superior laryngeal nerves were intact, but extended by the trauma. The pharynx and the vallecula were sutured, and an epithelialized tracheostoma was created by otolaryngological surgeons. The patient was given low-dose heparin intravenously (10,000 IU/d), but when he awoke, he had a left-sided partial hemiparesis. Two days postoperatively, a CT scan showed an ischemic infarct in the region perfused by the right middle cerebral artery (Fig 2), and color flow Doppler sonography was performed. In this examination, we observed an obliteration of the left carotid artery, but the right side was well perfused. Thus, no therapeutic consequence resulted.

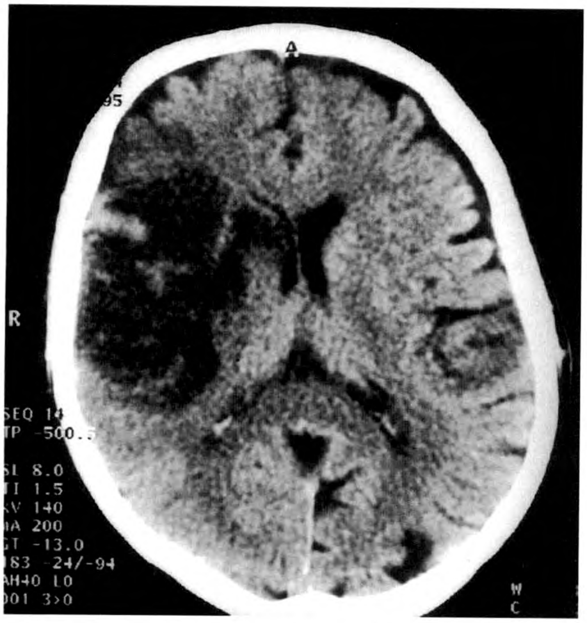


Fig 2. Computed tomography scan of brain, 1 day after hanging, showing infarct of that region of right cerebral hemisphere that is perfused by right middle cerebral artery.

Both vocal cords showed good mobility. When esophagography was performed with a water-soluble contrast medium 10 days postoperatively, the patient partially swallowed with aspiration, but this symptom improved slowly with intensive training. Neurologic deficits, too, slowly improved over the following months, leaving mild residual paresis of the forearm. Thus, due to prompt diagnostic measures and aggressive operative intervention, the patient survived with minimal functional deficit.

DISCUSSION

In suicidal hanging, the body usually does not fall from a high level. Therefore, the injuries rarely include dislocation or fracture of the cervical vertebrae. In a retrospective view of 35 cases of near-hanging, no cases of cervical spine fractures were found.[8] Death by hanging is usually due to occlusion of the nerves and vessels of the neck, especially in cases of partial suspension.[9] The mechanism of death in cases of complete suspension has been related to vagal stimulation by carotid sinus pressure, in addition to vascular and airway obstruction.[9] Death has also been caused by hemorrhage and edema formation in the larynx with fracture of the hyoid bone or laryngeal cartilages. Fracture of the hyoid bone or laryngeal cartilage as occurred in our patient has been found in 36% of suicidal hangings. Fractures are related to increasing age, and are not found when a soft ligature is employed.[10] In our patient, concurrent pharyngeal tears were diagnosed by direct endoscopy and immediately repaired. As hanging very often causes pharyngeal lesions,[8] endoscopy under general anesthesia should be performed in all cases of near-hanging.

Dissection of the common carotid artery has been reported to occur as a result of hanging.[11] In the reported case,[11] the patient complained of attacks of numbness of the left upper extremity that increased 2 years after the hanging. Angiography was performed and demonstrated an 80% stenosis of the right common carotid artery. Histologic findings revealed dissection of the medial layer of the arterial wall. The symptoms disappeared after endarterectomy. The authors concluded that the stenosis was not due to arteriosclerosis, but rather, to dissection as a result of hanging.

Hanging does not always result in death. Prompt release of the victim and aggressive resuscitation, even after prolonged periods of suspension and unconsciousness, increases the chance of survival.[12] As stated by Bautz and Knottenbelt,[13] initial care and resuscitation with intubation and ventilation are crucial. As unconsciousness, but not death, comes quickly after hanging, rapid diagnosis and therapy are required in comatose patients.[8,14] In our case, the length of time of suspension could not be ascertained. Although the patient was conscious at first, he quickly became stuporous, and later, unconscious. Carotid pulses were not palpable. A free interval before the onset of unconsciousness is typical in cases of blunt carotid trauma, as dissection of the intimal layer and progressive thrombosis can follow a blunt carotid trauma with a latency period of up to 24 hours.[15-17] Mooney and Bessen[18] described a case of late onset of cerebral symptoms 2 weeks after blunt carotid trauma. Besides cerebral ischemia following common or internal carotid artery occlusion, cerebral embolization from a thrombus in the artery may also be causal for neurologic symptoms and may explain the latency of the onset of deficits.[16] Intimal dissection can follow hyperextension or extreme flexion of the neck,[19] and thus, also, hanging. Therefore, after neurologic examination, intensive observation, CT scan of the head and neck, and repeated color flow Doppler sonography[20] are indicated in all patients who attempt suicide by hanging. If color flow Doppler sonography shows an intimal lesion, angiography and immediate surgery and reconstruction of the artery are indicated even if there is not yet a neurologic deficit.[16] Mears and Leonard[21] recommend angiography in all patients with neurologic symptoms, for cranial CT can be falsely negative. There is a common agreement that surgery is mandatory in patients with intimal lesions and no or only slight neurologic deficits, and in patients with progressive neurologic deterioration (stroke in evolution).[16,20] Contraindications to surgical intervention are controversial.[16,17,19-22] In a follow-up of all patients with carotid trauma in North Carolina from 1987 to 1993, Ramadan et al[20] describe a strikingly better outcome in those cases treated surgically as opposed to with conservative procedures. They recommend surgical treatment even in comatose patients. Brown et al[22] recommend revascularization in comatose patients when ischemia has been present only a short period of time before surgery (as in the case reported here). Some authors decline to use surgery in cases with long dissections of the carotid artery up to the skull base,[23] coma,[16] or severe neurologic symptoms.[24] They argue that those patients could sustain cerebral hemorrhage following revascularization.[16]

In our case, quick surgical intervention revealed bilateral occlusion of the carotid arteries that had already been diagnosed angiographically and resulted in relatively minor impairment of the patient. The intima was adapted to the medial layer of the arterial wall and partially resected. The left-sided partial hemiparesis slowly improved without leaving long-term compromise. No cerebral hemorrhage resulted from revascularization. This outcome confirms that coma is not a contraindication to surgery when there is a short latency between trauma and surgical intervention.[21]

CONCLUSION

Our case report shows that even in patients with unconsciousness accompanied by bilateral pulselessness and obstruction of the common carotid arteries, the compensatory circulation may be sufficient for a certain time to prevent permanent cerebral damage, given rapid diagnostic and therapeutic intervention. Thus, regardless of initial findings, rapid onset of diagnostic procedures and aggressive treatment of near-hanging victims should be initiated. As hanging may cause pharyngeal lesions, endoscopy under general anesthesia should be performed in all cases of near-hanging.

REFERENCES

1. Etzersdorfer E, Fischer P, Sonneck G. Epidemiology of suicide in Austria 1980-1990. Wien Klin Wochenschr 1992;104:594-9.

2. van Casteren V, van der Veken J, Tafforeau J, van Oyen H. Suicide and attempted suicide reported by general practitioners in Belgium, 1990-1991. Acta Psychiatr Scand 1993;87:451-5.

3. Diekstra RFW, van Egmond M. Suicide and attempted suicide in general practice, 1979-1986. Acta Psychiatr Scand 1989;79:268-75.

4. Anonymous. Suicide among children, adolescents, and young adults — United States, 1980-1992. JAMA 1995;274:451-2.

5. Sloan JH, Rivara FP, Reay DT, Ferris JA, Kellermann AL. Firearm regulations and rates of suicide. A comparison of two metropolitan areas. N Engl J Med 1990:322:369-73.

6. Bradshaw DA, Amundsen DE. Complications of suicidal hanging: a case report and brief review. Mil Med 1994;159:720-1.

7. Terazawa K, Akabane H, Nagao M, Wu B, Takatori T. An autopsy case of atypical hanging: were arteries and air passage obstructed? Jpn J Legal Med 1990;44:358-64.

8. van der Krol L, Wolfe R. The emergency department management of near-hanging victims. J Emerg Med 1994;12:285-92.

9. Elfawal MA, Awad OA. Deaths from hanging in the Eastern province of Saudi-Arabia. Med Sci Law 1994;34:307-12.

10. James R, Silcocks P. Suicidal hanging in Cardiff — a 15 year retrospective study. Forensic Sci Int 1992;56:167-75.

11. Noguchi K, Matsuoka Y, Hohda K, Katsuyama J, Nishimura S. A case of common carotid artery stenosis due to hanging. No Shinkei Geka 1992;20:1185-8.

12. Pradeep KG, Kanthaswamy V. Survival in hanging. Am J Forensic Med Pathol 1993;14:80-1.

13. Bautz P, Knottenbelt JD. Successful resuscitation from suicidal hanging: report of three cases. Injury 1994;25:111-2.

14. Brown VL, Espinosa J. Near-hanging injury: two case studies and an overview. J Emerg Nurs 1991;17:386-9.

15. Arseni C, Maretsis M, Dumitrescu L. Comments on the aetiology of indirect traumatic thrombosis of the internal carotid. Neurochirugia 1980;23:25-34.

16. Krajewski LP, Hertzer NR. Blunt carotid artery trauma. Report of two cases and review of the literature. Ann Surg 1980;191:341-6.

17. Dauber A, Hoffmann K, Zenker H, Hufen V. Bilateral carotid artery stenosis following severe craniocervical trauma. Chirurg 1991;62:433-6.

18. Mooney RP, Bessen HA. Delayed hemiparesis following nonpenetrating carotid artery trauma. Am J Emerg Med 1988;6:341-5.

19. Fabian TC, George SM, Croce MA, Mangiante EC, Voeller GR, Kudsk KA. Carotid artery trauma: management based on mechanism of injury. J Trauma 1990;30:953-61.

20. Ramadan F, Rutledge R, Oller D, Howell P, Baker C, Keagy B. Carotid artery trauma: a review of contemporary trauma center experiences. J Vasc Surg 1995;21:46-56.

21. Mears GD, Leonard RB. Blunt carotid trauma: a case report. J Emerg Med 1988;6:281-4.

22. Brown MF, Graham JM, Feliciano DV, Mattox KL, Beall AC, De Bakey ME. Carotid artery injuries. Am J Surg 1982;144:748-53.

23. Richardson JD, Simpson C, Miller FB. Management of carotid artery trauma. Surgery 1988;104:673-80.

24. Davis JW, Holbrook TL, Hoyt DB, MacKersie RC, Field TO, Shackford SR. Blunt carotid artery dissection: incidence, associated injuries, screening, and treatment. J Trauma 1990;30:1514-7.

DECREASE OF SERUM LEVELS OF SOLUBLE CD23 DURING IMMUNOTHERAPY IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

AYAKI TANAKA, MD
YOSHIHIRO OHASHI, MD
YOSHIAKI NAKAI, MD
OSAKA, JAPAN

There is increasing in vitro evidence that soluble CD23 (sCD23) is capable of potentiating the synthesis of human IgE and is likely involved in the expression of allergic diseases. Our study has aimed at investigating whether serum sCD23 is elevated in patients with perennial allergic rhinitis as compared to nonatopic controls, whether sCD23 in perennial allergic rhinitis fluctuates during the natural course in untreated patients, and whether sCD23 is decreased by immunotherapy. This study included 139 patients with perennial allergic rhinitis due to *Dermatophagoides farinae* who gave informed consent to participation. They were divided into 2 groups — an untreated group and an immunotherapy group — according to their treatment background. Thirty-one nonallergic, healthy volunteers were included to serve as controls. Symptom scores and serum concentrations of IgE specific to *D farinae* and sCD23 were examined twice in each patient: at enrollment (first evaluation) and on a variant time course after enrollment (second evaluation). Serum concentrations of sCD23 were measured by a sandwich enzyme-linked immunosorbent assay. The level of sCD23 in patients with perennial allergic rhinitis was significantly higher than that in nonatopic controls ($p < .0001$). The level of sCD23 in perennial allergic rhinitis was correlated with the level of specific IgE against *D farinae.* The sCD23 level did not fluctuate during the natural course for a span of 2.8 ± 2.7 years in untreated patients ($p = .1337$), but was significantly decreased in patients who received immunotherapy for 2.7 ± 2.2 years ($p < .0001$). The rate of decrease in sCD23 was significantly correlated with the rate of decrease in specific IgE ($r_s = .523$, $p < .0001$) and symptom scores ($r_s = .450$, $p < .0001$). In conclusion, the reduction in sCD23 during immunotherapy is probably related to the decrease in specific IgE and also plays a role in mediating its clinical effect.

KEY WORDS — immunotherapy, perennial allergic rhinitis, soluble CD23, specific IgE.

INTRODUCTION

CD23 (FcεRII) is a low-affinity receptor for IgE that is found on multiple cells, including lymphocytes, monocytes, and eosinophils.[1,2] Recent evidence suggests that CD23 may be involved in B cell activation and antigen presentation to T cells,[2] although the function of CD23 on cells is likely to depend on which cell type expressed it. An augmentation of the number of CD23-bearing cells and of the cellular density of CD23 has been documented in patients with allergic[3,4] and parasitic diseases,[5] as well as other hyper-IgE states.[6]

Soluble CD23 (sCD23) is released after a series of proteolytic steps, and is also known as an IgE-binding factor.[2,7,8] There is increasing in vitro evidence that sCD23 is capable of potentiating the synthesis of human IgE[9-13] and is likely involved in the expression of allergic diseases. Anti-CD23 antibodies can inhibit both ongoing and interleukin (IL)–4–stimulated IgE synthesis,[10-12] and the supernatant from the RPMI 1886 cell line, which contains relatively large amounts of CD23 materials, can enhance IgE production from lymphocytes of atopic individuals.[13]

However, the in vivo physiologic significance of sCD23 remains to be fully established. Elevated serum levels of sCD23 have been reported in atopic patients,[14-17] although the correlation was weak[15-17] or not significant[14] between total IgE and sCD23 in serum. The specific IgE level is more important in allergic diseases than the total IgE level. However, possible correlation between the relevant or specific IgE and sCD23 in patients with allergic diseases has yet to be discussed. In addition, elevated serum levels of sCD23 in atopic individuals may be affected by active treatments such as allergen-specific immunotherapy, because immunotherapy can decrease specific IgE in serum.[18,19] Our study is therefore aimed at investigating the serum levels of sCD23 in patients with perennial allergic rhinitis due to *Dermatophagoides farinae,* with special reference to possible modulation by allergen-specific immunotherapy.

MATERIALS AND METHODS

PATIENTS

This study included 31 nonatopic healthy volun-

From the Department of Otolaryngology, Osaka City University Medical School, Osaka, Japan. Supported by a Grant-in-Aid for Scientific Research (07671878) from the Ministry of Education, Science and Culture of Japan.

CORRESPONDENCE — Yoshihiro Ohashi, MD, Dept of Otolaryngology, Osaka City University Medical School, 1-4-3 Asahimachi, Abeno, Osaka 545-8585, Japan.

teers (13 women and 18 men, nonatopic group) and 139 patients (56 women and 83 men) with perennial allergic rhinitis due to *D farinae* who gave informed consent to participation in our protocol to study long-term immunologic changes in allergic rhinitis. This study design followed the principles outlined in the Declaration of Helsinki.[20] They were divided into 2 groups — an untreated group and an immunotherapy group — according to their treatment background. The 95 patients (38 women and 57 men) of the immunotherapy group served to investigate possible changes in serum levels of sCD23 during immunotherapy, and the 44 patients (18 women and 26 men) of the untreated group served to investigate natural changes in serum levels of sCD23.

Immunotherapy Group. The immunotherapy group included 95 patients (38 women and 57 men). All the patients of the immunotherapy group were selected from our outpatients who satisfied all of the following conditions before immunotherapy: 1) a well-documented history of perennial allergic rhinitis and no seasonal aggravation during pollen seasons, 2) no history of asthma, 3) positive skin test and positive nasal provocation to *D farinae* before immunotherapy, 4) a negative skin test and negative nasal provocation to other major aeroallergens in Japan such as Japanese cedar pollen, ragweed, Japanese cypress pollen, and molds, 5) eosinophilia in nasal smears before immunotherapy, and 6) a serum sample that was previously collected before immunotherapy and stored at –60°C. They started to receive immunotherapy immediately after enrollment, using Hollister-Stier standardized *D farinae* (Miles Inc, USA) for their nasal symptoms. The age range was between 15 and 51 years old (mean 29.7 years; standard deviation [SD] 9.9 years; standard error [SE] 1.0 years) at the time of enrollment.

The patients of the immunotherapy group were further divided into the following 2 subgroups based on their periods of immunotherapy: the short-term immunotherapy group (38 patients), who were treated for 1 year with immunotherapy, and the long-term immunotherapy group (57 patients), who were treated for more than 2 years with immunotherapy.

Untreated Group. The untreated group included 44 patients with perennial allergic rhinitis due to *D farinae*. The patients were between 15 and 49 years old (mean 29.3; SD 9.1; SE 1.4) at the time of enrollment. All the patients of the untreated group satisfied each of the following conditions before enrollment: 1) a well-documented history of perennial allergic rhinitis due to *D farinae*, 2) no history of asthma, 3) positive skin tests and positive nasal provocations to *D farinae*, 4) eosinophilia in nasal smears before enrollment, 5) no previous immunotherapy, and 6) a serum sample that was collected at enrollment and stored at –60°C. The patients of the untreated group were allowed to take rescue medicines such as antihistamine tablets for their nasal symptoms, if necessary.

Nonatopic Group. The 31 volunteers of the nonatopic group, matched for age and sex with the patients, were chosen on the basis of the following criteria: 1) no history of allergic disease, 2) no physical findings indicative of atopic diseases, and 3) negative serum IgE antibodies specific to major allergens in Japan, such as house dust mites, Japanese cedar pollen, ragweed, Japanese cypress pollen, and molds. The age range was between 15 and 64 years (mean 29.5; SD 11.4; SE 2.0) at the time of enrollment.

MODE OF IMMUNOTHERAPY

The patients of the immunotherapy group were given subcutaneous injections of Hollister-Stier standardized *D farinae* (Miles Inc, USA), with a prior full explanation about immunotherapy for allergic rhinitis. The details of the immunotherapy employed in this study are described elsewhere.[18,19] In brief, the individual initiative dose was determined by threshold skin tests. Doses were increased by 50% at weekly intervals until the individual maximum tolerated dose was reached. The maximum tolerated dose was attained in 4 to 8 months with the once-weekly program. The maximum tolerated dose was 3,000 allergen units in 72 of the 95 patients. Then, a weekly injection of this dose was continued for the first few months after attainment of the maintenance dose. They then received injections of this dose on a biweekly basis for the next few months, and then monthly injections. Finally, the interval between injections was gradually increased up to 2 months in the absence of an episode of symptomatic relapse. After each injection, the patient was asked to remain under our supervision for a minimum of 30 minutes and to report any symptoms that they experienced. No concomitant medication affecting nasal symptoms was admitted throughout the period, with prior informed consent. All the patients intentionally continued the treatment to avoid possible relapse even though they had no more nasal symptoms.

STUDY DESIGN

Nasal symptoms and serum concentrations of IgE specific to *D farinae* and of sCD23 were examined twice in each patient: at enrollment (first examination) and at a variant time after the enrollment (second examination). The second examination was performed in each patient in the same month the first examination was done, to avoid possible seasonal fluctuation of house dust mite levels. The mean intervals between the examinations were 2.7 years (SD 2.2; SE 0.2; range 1 to 12) in the immunotherapy group and 2.8 years (SD 2.7; SE 0.4; range 1 to 13) in the untreated group. As for the nonatopic group, serum concentrations of specific IgE and sCD23 were determined once in each individual.

The clinical evaluation used in this study was based on our criteria and daily symptom diary cards. The details of the method employed in this study have been described elsewhere.[18,19] In brief, all patients were asked to complete daily symptom diary cards in the 14 days before the assessment of nasal symptom scores. The daily symptom card includes the number of sneezing attacks, the frequency of nose blowing, and the degree of nasal obstruction. A careful survey of the diary card graded the 3 nasal symptoms (sneeze, rhinorrhea, and obstruction) on a scale of 0 to 3, depending on severity. The average daily sum of the 3 nasal symptom scores was used as the symptom score (maximum 9). The rate of decrease in the symptom score following enrollment was calculated with the following formula: Rate of decrease in symptom score = [(symptom score at the first examination – symptom score at the second examination)/symptom score at the first examination] × 100.

Specific IgE antibodies and sCD23 in serum were determined at the same time. IgE specific to *D farinae* was measured by the CAP radioallergosorbent test. Serum concentrations of sCD23 were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) with the use of 2 monoclonal antibodies that recognize different epitopes of CD23. The details of the method employed in this study are described elsewhere[21]; it was a modification of the method previously described by Yanagihara et al.[22] The methodology and justification of the method and monoclonal antibodies employed in this study have been described elsewhere.[22] The minimum sensitivity for this assay was 40 U/mL of sCD23.

The rates of decrease in specific IgE and sCD23 were calculated with the following formula: Rate of decrease in specific IgE or sCD23 = [(value at the first examination – value at the second examination)/ value at the first examination] × 100.

STATISTICAL ANALYSIS

In this study, all levels were expressed as mean ± SD. For comparisons between different groups, the Mann-Whitney U-test was used. For comparisons of paired values, Wilcoxon's signed-rank test was used. Differences were considered significant when $p < .05$. Spearman's correlation coefficient (r_s) was calculated to determine the degree of correlation between 2 different parameters, and significant correlation was accepted when $p < .05$ on Spearman's rank correlation analysis.

RESULTS

BACKGROUND OF SUBJECTS

There were no sex differences among the nonatopic group, the untreated group, and the immunotherapy group. The ages at enrollment were not significantly different among the 3 groups (nonatopic group versus untreated group, p = .7385; nonatopic group versus immunotherapy group, p = .9386; untreated group versus immunotherapy group, p = .6998). The intervals between the first and second examinations were not significantly different between the untreated group and the immunotherapy group (p = .7756).

NONATOPIC GROUP

IgE specific to *D farinae* was not detected in any individual of the nonatopic group. The serum level of sCD23 was 185.5 ± 43.1 U/mL in the nonatopic group.

UNTREATED GROUP

The symptom score and levels of specific IgE and sCD23 at the first examination were 4.6 ± 1.3, 32.6 ± 35.6 U/mL, and 271.2 ± 108.5 U/mL, respectively. The level of sCD23 in the untreated group was significantly higher than that in the nonatopic group (p = .0004; Fig 1). The symptom score was not significantly correlated with the level of specific IgE or the level of sCD23 at the first examination (symptom score versus specific IgE, $r_s = -.145$, p = .2274; symptom score versus sCD23, $r_s = -.005$, p = .7991). However, a significant correlation between the sCD23 level and the specific IgE level was observed at the first examination ($r_s = .387$, p = .0113).

The symptom score and levels of specific IgE and sCD23 at the second examination were 4.4 ± 1.6, 33.7 ± 35.9 U/mL, and 279.6 ± 113.3 U/mL, respectively. The level of sCD23 in the untreated group at the second examination was significantly higher than that in the nonatopic group (p = .0002; Fig 1). The symptom score was not significantly correlated with the level of specific IgE or the level of sCD23 at the second examination (symptom score versus specific IgE, $r_s = .068$, p = .7515; symptom score versus sCD23, $r_s = .187$, p = .2632). However, a significant correlation was observed between the sCD23 level and the specific IgE level at the second examination ($r_s = .330$, p = .0308).

Neither the symptom score nor specific IgE nor

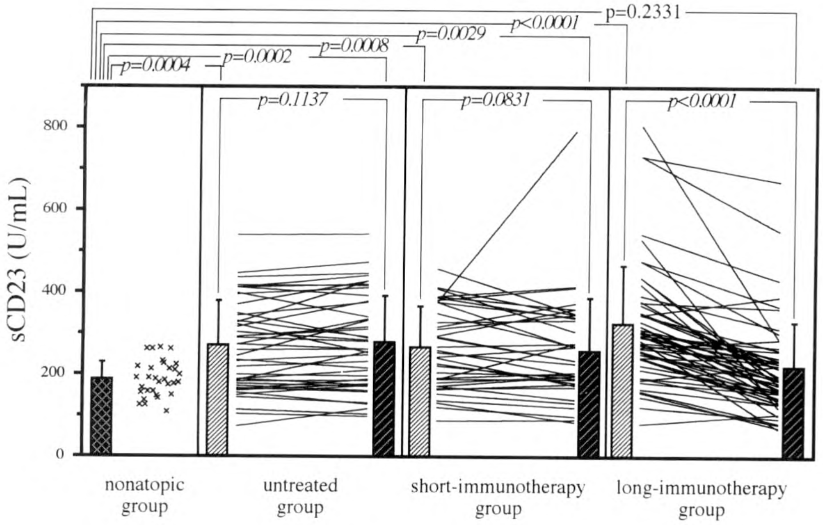


Fig 1. Serum levels of soluble CD23 (sCD23). Levels of sCD23 at first examination (lighter bars) in untreated group, short-immunotherapy group, and long-immunotherapy group were significantly higher than that in nonatopic group. No significant change in sCD23 level was observed in untreated group or in short-immunotherapy group. In contrast, significant decrease in sCD23 level was observed in long-immunotherapy group. Additionally, sCD23 level at second examination (darker bars) in long-immunotherapy group, but not in untreated group or in short-immunotherapy group, was not different from that in nonatopic group.

sCD23 differed significantly between the first and second examinations (symptom score, p = .8055; specific IgE, p = .0630, Fig 2; sCD23, p = .1137, Fig 1).

IMMUNOTHERAPY GROUP

The symptom score and levels of specific IgE and sCD23 at the first examination were 7.6 ± 1.2, 28.4 ± 31.4 U/mL, and 301.2 ± 128.9 U/mL, respectively. The symptom score at the first examination in the immunotherapy group was significantly higher than that in the untreated group (p < .0001). The sCD23 level in the immunotherapy group at the first examination was significantly higher than that in the nonatopic group (p < .0001). The symptom score was not significantly correlated with the level of specific IgE or the level of sCD23 at the first examination (symptom score versus specific IgE, r_s = .085, p = .6009; symptom score versus sCD23, r_s = .020, p = .8954). However, a significant correlation between the sCD23 level and specific IgE level was observed at the first examination (r_s = .360, p = .0005).

The symptom score and levels of specific IgE and sCD23 at the second examination were 2.8 ± 1.9, 26.3 ± 32.8 U/mL, and 235.7 ± 118.3 U/mL, respectively. The sCD23 level in the immunotherapy group at the second examination was still significantly higher than that in the nonatopic group (p = .0300). The symptom score was not significantly correlated with the specific IgE level or the sCD23 level at the second examination (symptom score versus specific IgE, r_s = .085, p = .6009; symptom score versus sCD23, r_s = .220, p = .0524). However, a significant correlation was observed between the sCD23 level and the specific IgE level at the second examination (r_s = .329, p = .0014).

The symptom score and levels of specific IgE and sCD23 were significantly lower at the second examination than at the first examination (symptom score, p < .0001; specific IgE, p = .0020; sCD23, p < .0001). The rates of decrease were significantly correlated with the duration (years) of immunotherapy (symptom score, r_s = .558, p < .0001; specific IgE, r_s = .669, p < .0001; sCD23, r_s = .693, p < .0001; Fig 3). The rates of decrease were significantly correlated with each other (symptom score versus specific IgE, r_s = .349, p = .0008; symptom score versus sCD23,

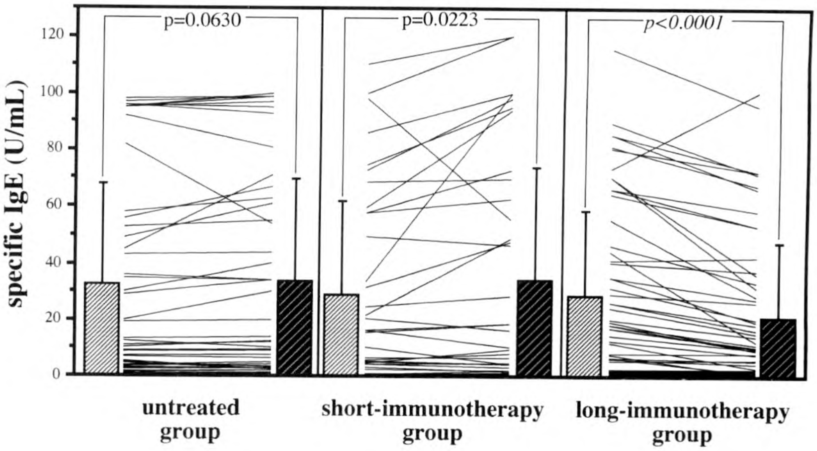


Fig 2. Serum levels of specific IgE. No significant change in specific IgE level was observed in untreated group. In contrast, significant increase in specific IgE level was observed in short-immunotherapy group, and significant decrease in specific IgE level was observed in long-immunotherapy group. Lighter bars — first examination; darker bars — second examination.

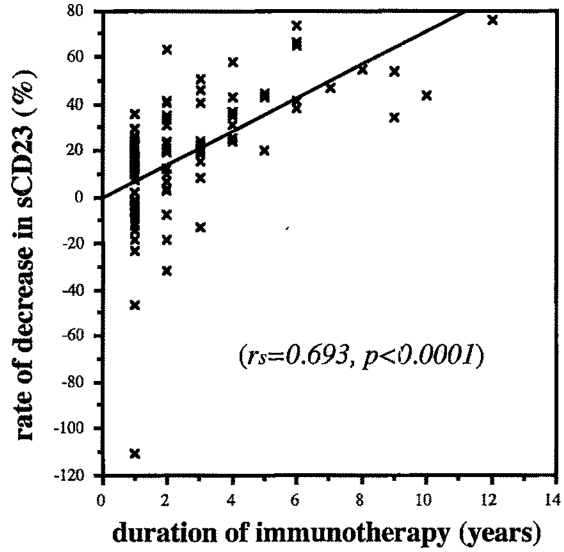


Fig 3. Diagram of correlation between rate of decrease in sCD23 and duration of immunotherapy. Rate of decrease in sCD23 was significantly correlated with duration of immunotherapy.

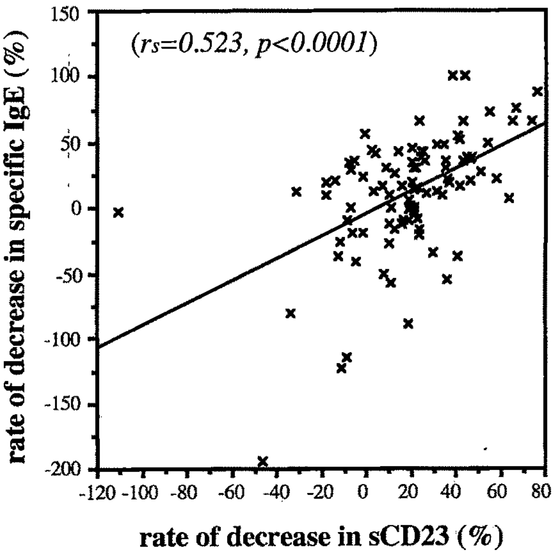


Fig 4. Diagram of correlation between rate of decrease in specific IgE and rate of decrease in sCD23 in immunotherapy group. Rate of decrease in sCD23 was significantly correlated with rate of decrease in specific IgE.

rs = .450, p < .0001; specific IgE versus sCD23, rs = .523, p < .0001; Fig 4).

Short-Immunotherapy Group. The symptom score at the second examination was significantly smaller than that at the first examination (first examination, 7.6 ± 1.3; second examination, 3.7 ± 1.8; p < .0001). The level of specific IgE was significantly higher at the second examination than at the first examination (first examination, 28.6 ± 33.5 U/mL; second examination, 34.0 ± 39.9 U/mL; p = .0223; Fig 2), but the levels of sCD23 did not differ significantly between the first and the second examinations (first examination, 265.9 ± 99.4 U/mL; second examination, 259.4 ± 127.8 U/mL; p = .0831; Fig 1). The levels of sCD23 at the first and second examinations in the short-immunotherapy group were significantly higher than that in the nonatopic group (first examination; p = .0008; second examination, p = .0029; Fig 1).

Long-Immunotherapy Group. The symptom score and levels of specific IgE and sCD23 were significantly smaller at the second examination than at the first examination (symptom score, 7.6 ± 1.2 at the first examination and 2.2 ± 1.8 at the second examination, p < .0001; specific IgE, 28.3 ± 30.2 U/mL at the first examination and 21.2 ± 26.2 U/mL at the second examination, p < .0001, Fig 2; sCD23, 324.8 ± 141.2 U/mL at the first examination and 219.9 ± 109.8 U/mL at the second examination, p < .0001, Fig 1). The sCD23 level in the long-immunotherapy group at the first examination was significantly higher than that in the nonatopic group (p < .0001), but the sCD23 level at the second examination was not significantly different from that in the nonatopic group (p = .2331, Fig 1).

COMPARISON BETWEEN UNTREATED GROUP AND IMMUNOTHERAPY GROUP

At the first examination, the levels of specific IgE and sCD23 did not differ significantly between the untreated group and the immunotherapy group (specific IgE, p = .4998; sCD23, p = .2692), but the symptom score was significantly higher in the immunotherapy group than in the untreated group (p < .0001). The rates of decrease in symptom score, specific IgE, and sCD23 were significantly larger in the immunotherapy group than in the untreated group (symptom score, p < .0001; specific IgE, p = .0004; sCD23, p < .0001).

COMPARISON BETWEEN SHORT-IMMUNOTHERAPY GROUP AND LONG-IMMUNOTHERAPY GROUP

At the first examination, the symptom scores and levels of specific IgE and sCD23 did not differ significantly between the short-immunotherapy group and the long-immunotherapy group (symptom scores, p = .8320; specific IgE, p = .7296; sCD23, p = .0606). The rates of decrease in symptom scores, specific IgE, and sCD23 were significantly larger in the long-immunotherapy group than in the short-immunotherapy group (symptom scores, p = .0002; specific IgE, p < .0001; sCD23, p < .0001).

DISCUSSION

The first purpose of this study was to examine whether serum levels of sCD23 in patients with perennial allergic rhinitis were higher than those in nonatopic controls. The serum level of sCD23 shows a marked age-dependent variation; it is highest in infants and then decreases gradually with age.[17] In our study, all the subjects were 15 or more years old at enrollment, and there was no significant difference in ages among the nonatopic group, the untreated group, and the immunotherapy group. The serum levels of sCD23 in both the untreated group and the immunotherapy group at enrollment were significantly higher than those in the nonatopic group. These results clearly suggest that sCD23 levels before treatment are elevated in patients with perennial allergic rhinitis. Elevated serum levels of sCD23 have been reported in atopic patients by several investigators,[14-17] although the correlation between total IgE and sCD23 was weak[15-17] or not significant.[14] To the best knowledge of the authors, correlation between sCD23 and specific IgE has yet to be discussed. In our study, the levels of sCD23 before treatment were significantly correlated with the levels of specific IgE in patients with perennial allergic rhinitis. This is the first documentation of a significant correlation between specific IgE levels and sCD23 levels in patients with allergic diseases. However, the levels of sCD23, like those of specific IgE, before treatment were not significantly correlated with the symptom scores.

It is also of clinical interest whether higher levels of serum sCD23 in perennial allergic rhinitis could be modulated by medical treatment. The immunologic activation and inflammatory process in airway allergic diseases might be modulated by specific and active treatment. Since immunotherapy is an active treatment, unlike conventional drug treatments, this therapeutic method may modulate immunologic abnormalities occurring in allergic diseases. Indeed, immunotherapy is reported to reduce specific IgE synthesis in perennial allergic rhinitis.[18,19] This reduction of specific IgE synthesis might be related to a possible decrease in sCD23 by immunotherapy. Our second aim was thus to study the effect of immunotherapy on the sCD23 level. Possible effects of medical treatment on sCD23 in patients with allergic diseases were previously discussed by Yanagihara et al,[15] who compared sCD23 levels in patient groups under various treatments with an untreated patient group. The sCD23 levels in patients receiving immunotherapy or local steroids were not significantly different from those in untreated subjects, but subjects receiving systemic steroids had significantly lower levels of sCD23 than the untreated subjects.[15] Their data may suggest that sCD23 could be decreased by systemic steroids, but not by immunotherapy. However, such discussions based on group comparison may lead to confusing conclusions, because pretreatment values are considerably different among individual patients.

Before discussing the possible modulation of sCD23 levels by immunotherapy, we must know the natural changes in serum levels of sCD23 in untreated patients with perennial allergic rhinitis. If sCD23 levels fluctuate in untreated patients, an increase or a decrease in sCD23 levels in patients on immunotherapy may be the result of an immunotherapy-independent phenomenon. We thus studied the natural course of sCD23 levels in untreated patients with perennial allergic rhinitis. They were not treated for their perennial nasal symptoms after enrollment, except for sporadic use of rescue antihistamine tablets. Serum samples were collected in the same month in each patient, to avoid the possible influence of a seasonal variation in house dust mites. Therefore, our study design can appropriately discuss the natural changes in specific IgE and sCD23 for a span of 2.8 ± 2.7 years in untreated patients with perennial allergic rhinitis. In the untreated group, sCD23 levels were not significantly different between the first and second examinations. Our results thus suggest that sCD23 levels do not fluctuate significantly during the natural course for a span of 2.8 ± 2.7 years. Also, no significant changes were observed in specific IgE levels, in line with our previous report.[23]

Next, we studied whether immunotherapy could decrease serum levels of sCD23 in patients with perennial allergic rhinitis. The duration between the first examination (before immunotherapy) and the second examination (after immunotherapy) in the immunotherapy group was 2.7 ± 2.2 years, which was not significantly different from that in the untreated group. The sCD23 levels after a year of immunotherapy were not significantly different from their pretreatment levels ($p = .0831$) and were still higher than those in the nonatopic group ($p = .0029$). In contrast, the sCD23 levels were significantly decreased after 2 or more years of immunotherapy ($p < .0001$) and did not differ significantly from those of the nonatopic group ($p = .2331$). The rate of decrease in sCD23 was significantly correlated with the duration of immunotherapy ($r_s = .693$, $p < .0001$). Our findings therefore suggest that a year of immunotherapy cannot affect serum levels of sCD23 in patients with perennial allergic rhinitis, but that 2 years of immunotherapy are able to significantly decrease serum levels of sCD23.

Our previous studies have demonstrated that immunotherapy is able to attenuate specific IgE and, additionally, to switch the preferential IgE response to an IgG response.[18,19] In our present study, changes in specific IgE levels were also investigated in the untreated group and in the immunotherapy group. Specific-IgE levels were not changed in the untreated group, but were significantly decreased in the immunotherapy group. In addition, the rate of decrease in specific IgE was significantly correlated with the rate of decrease in sCD23 in the immunotherapy group. It is therefore likely that the decrease in sCD23 is probably related to the decrease in specific IgE during immunotherapy.

Serum levels of sCD23 were not correlated with the symptom scores before ($p = .8954$) or after immunotherapy ($p = .0524$). In addition, at enrollment, the levels of sCD23 were not significantly different between the untreated group and the immunotherapy group, although symptom scores were much larger in the immunotherapy group. Therefore, sCD23 levels probably have little relationship with the symptomatic severity of perennial allergic rhinitis. Of interest, however, the magnitude of the decrease in sCD23 was significantly correlated with the magnitude of the decrease in symptom scores ($p < .0001$). These findings could be interpreted to mean that an immunotherapy-induced decrease in sCD23 plays a role in mediating its clinical effect.

In conclusion, serum levels of sCD23 were elevated in patients with perennial allergic rhinitis compared to nonatopic individuals, and the levels of sCD23 were correlated with the levels of specific IgE. The level of sCD23 in perennial allergic rhinitis did not fluctuate during the natural course, but was significantly decreased during the course of immunotherapy. This reduction in sCD23 during immunotherapy is probably related to the decrease in specific IgE and is also probably involved in clinical improvement during immunotherapy.

Our study has demonstrated that immunotherapy can decrease serum levels of sCD23 in perennial allergic rhinitis, but the effect of immunotherapy on sCD23 levels in patients allergic to Hymenoptera venom was different, as reported by Forman et al.[24] In their study, sCD23 levels in 15 patients were determined before and at variable times during immunotherapy (mean duration, 54 months), and sCD23 levels were found to be unchanged over the course of venom immunotherapy. In addition, their patients had lower mean sCD23 levels when compared with nonatopic controls. The clinical role of sCD23 might be quite different in venom allergy as opposed to perennial allergy due to house dust mites.

ACKNOWLEDGMENTS — The authors acknowledge the important technical assistance of Yoshiharu Ohno, MD, Hirokazu Sakamoto, MD, Akifumi Kato, MD, Tateo Masamoto, MD, Yasushi Kakinoki, MD, and Yushi Washio, MD, in the Department of Otolaryngology, Osaka City University Medical School.

REFERENCES

1. Spiegelberg HL, O'Connor RD, Simon RA, Mathison DA. Lymphocytes with immunoglobulin E Fc receptors in patients with atopic disorders. J Clin Invest 1979;64:714-20.

2. Gordon J, Flores-Romo L, Cairns JA, et al. CD23 a multifunctional receptor/lymphokine? Immunol Today 1989;10:153-7.

3. Spiegelberg HL. The expression of IgE Fc receptors on lymphocytes of allergic patients. Int Rev Immunol 1987;2:63-71.

4. Suemura M, Kishimoto J. IgE class-specific regulatory factors and Fce receptors on lymphocytes. Int Rev Immunol 1987;2:27-42.

5. Watanabe N, Yanagihara Y, Joh K, Hamada A, Tomita Y, Kobayashi A. Fc-epsilon-receptor-bearing lymphocytes in patients with clonorchiasis. Int Arch Allergy Appl Immunol 1989; 89:103-7.

6. Nagai T, Adachi M, Noro N, Yodoi J, Uchida H. T and B lymphocytes with immunoglobulin E Fc receptors (FceR) in patients with nonallergic hyperimmunoglobulinemia E: demonstration using a monoclonal antibody against FceR-associated antigen. Clin Immunol Immunopathol 1985;35:261-75.

7. Conrad DH. The low affinity receptor for IgE. Annu Rev Immunol 1990;8:623-45.

8. Letellier M, Nakajima T, Pulido-Cejudo G, Hofstetter H, Dellespesse G. Mechanism of formation of human IgE-binding factors (soluble CD23). III. Evidence for a receptor (FceRII)-associated proteolytic activity. J Exp Med 1990;172:693-700.

9. Sarfati M, Rector E, Wong K, Rubio-Truijillo M, Sehon AH, Delespesse G. In vitro synthesis of IgE by human lymphocytes. II. Enhancement of the spontaneous IgE synthesis by IgE-binding factors secreted by RPMI 8866 lymphoblastoid B cells. Immunology 1984;53:197-205.

10. Sarfati M, Delespesse G. Possible role of human lymphocyte receptor for IgE (CD23) or its soluble fragments in the in vitro synthesis of human IgE. J Immunol 1988;141:2195-9.

11. Pene J, Rousset F, Briere F, et al. Interleukin 5 enhances interleukin 4-induced IgE production by normal human B cells: the role of soluble CD23 antigen. Eur J Immunol 1988;18:929-35.

12. Pene J, Chretien I, Rousset F, Briere F, Bonnefoy JY, de Vries JE. Modulation of IL-4-induced human IgE production in vitro by IFN-γ and IL-5: the role of soluble CD23 (sCD23). J Cell Biochem 1989;39:253-64.

13. Saxon A, Ke Z, Bahati L, Stevens RH. Soluble CD23 containing B cell supernatants induce IgE from peripheral blood B-lymphocytes and costimulate with interleukin-4 in induction of IgE. J Allergy Clin Immunol 1990;86:333-44.

14. Matsumoto T, Miike T, Yamaguchi K, Murakami M, Kawabe T, Yodoi J. Serum levels of soluble IL-2 receptor, IL-4 and IgE-binding factors in childhood allergic diseases. Clin Exp Immunol 1991;85:282-92.

15. Yanagihara Y, Sarfati M, Marsh D, Nutman T, Delespesse G. Serum levels of IgE-binding factor (soluble CD23) in diseases associated with elevated IgE. Clin Exp Allergy 1990;20:395-401.

16. Reddy MM, Weissman AM, Mazza DS, Meriney DK, Johns M, Grieco MH. Circulating elevated levels of soluble CD23, interleukin-4, and CD20+CD23+ lymphocytes in atopic subjects with elevated serum IgE concentrations. Ann Allergy 1992;69:131-4.

17. Kim KM, Nanbu M, Iwai Y, et al. Soluble low affinity Fc receptors for IgE in the serum of allergic and nonallergic children. Pediatr Res 1989;26:49-53.

18. Ohashi Y, Nakai Y, Okamoto H, et al. Serum level of interleukin-4 in patients with perennial allergic rhinitis during allergen-specific immunotherapy. Scand J Immunol 1996;43: 680-6.

19. Ohashi Y, Nakai Y, Okamoto H, et al. Significant correlation between symptom score and IgG4 antibody titer following long-term immunotherapy for perennial allergic rhinitis. Ann Otol Rhinol Laryngol 1997;106:483-9.

20. 41st World Medical Assembly. Declaration of Helsinki: recommendations guideline for physicians in biomedical research involving human subjects. Bull Pan Am Health Organ 1990;24:606-9.

21. Ohashi Y, Nakai Y, Kakinoki Y, et al. Immunotherapy affects the seasonal increase in specific IgE and interleukin-4 in serum of patients with seasonal allergic rhinitis. Scand J Immunol 1997;46:67-77.

22. Yanagihara Y, Kiniwa M, Kajiwara K, Shida T. Establishment of a sensitive radioimmunoassay for the detection of human IgE-binding factor (soluble CD23). Int Arch Allergy Immunol 1992;98:189-99.

23. Ohashi Y, Nakai Y, Ohno Y, et al. Natural course of serum specific IgE and IgG4 for a span of eight years in untreated patients with perennial allergic rhinitis. Laryngoscope 1997;107: 382-5.

24. Forman SO, Reddy MM, Mazza DS, Meriney DK, Grieco MH. Effect of immunotherapy on sCD23 levels in patients allergic to Hymenoptera venom. Ann Allergy Asthma Immunol 1996;77:282-4.

≈

RECENT ADVANCES IN OTITIS MEDIA

The 7th International Symposium on Recent Advances in Otitis Media will be held June 1-5, 1999, in Fort Lauderdale, Florida. For information, contact David J. Lim, MD, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057.

Ann Otol Rhinol Laryngol 108:1999

PATULOUS EUSTACHIAN TUBE IN LONG-TERM SURVIVORS OF NASOPHARYNGEAL CARCINOMA

PO-WEN CHENG, MD

YI-HO YOUNG, MD

PEI-JEN LOU, MD

TAIPEI, TAIWAN

This article reports on 21 long-term (10 years) survivors of nasopharyngeal carcinoma, divided into 2 groups: those subjected to an inflation-deflation test and a clearance function test in a longitudinal study, and those receiving sonotubometry in a cross-sectional study. On the inflation-deflation test, 12 (55%) out of 22 ears had a patulous eustachian tube, and on sonotubometry, 10 (50%) out of 20 ears also revealed a patulous eustachian tube. Except for 4 ears with chronic otitis media, the ears had resolved to a normal eardrum appearance at 10 years postirradiation. The phenomenon might be attributed to both restoration of the impaired tubal function and the development of a patulous tube.

KEY WORDS — nasopharyngeal carcinoma, patulous eustachian tube, postirradiation outcome, radiotherapy.

INTRODUCTION

Our previous studies have examined eustachian tube function (ETF) in patients with nasopharyngeal carcinoma (NPC) before radiotherapy.[1,2] According to those results, tubal dysfunction was noted in 90% of NPC patients before radiotherapy. Such a high percentage was attributed to functional impairment rather than organic obstruction of the tube. During that time, no patulous eustachian tube was noted in any ear. Twenty patients were subjected to an ETF test 5 years after radiotherapy, disclosing that the dynamic ETF had recovered to a normal range in most ears if the radiation dosage was not more than 70 Gy.[3] However, a patulous tube was still not found in this period. In 1996, these NPC patients had survived for 10 years after radiotherapy. This study examines the effects of irradiation on tubal function, hearing, and the middle ear condition in long-term survivors of NPC via longitudinal and cross-sectional studies.

STUDY I: INFLATION-DEFLATION TEST AND CLEARANCE FUNCTION TEST

Patients and Methods. Among the 14 long-term (10 years) survivors of NPC, 11 (22 ears) patients agreed to receive an ETF test again. If the eardrum was intact, myringotomy was performed, with the patient's consent, to observe the middle ear condition, followed by an inflation-deflation test. Instruments consisted of a transducer, an amplifier (SEN-6102, Nihon Koden), and a recorder (SR-6411, Graphtec). The normal (mean ± SD) passive opening pressure in our laboratory was 364 ± 222 mm H_2O.[2] If the opening pressure exceeded 586 mm H_2O, the tube was regarded as blocked; below 142 mm H_2O, it was considered patulous.

The positive pressure test result was considered normal when the applied pressure (+200 mm H_2O) dropped below +100 mm H_2O after several swallowings. The result was considered poor when the applied pressure did not drop below +100 mm H_2O. The tube was considered patulous when the applied pressure (+100 mm H_2O) could not be maintained. The negative pressure test result was considered normal when the applied pressure (–200 mm H_2O) dropped below –200 mm H_2O after several swallowings. The result was considered poor when the applied pressure showed no change. The tube was considered patulous when the applied pressure (–100 mm H_2O) could not be maintained. When both the passive opening pressure test and the active opening pressure test (including positive and negative pressure tests) revealed a patulous tube, the tube was rated as patulous.

A clearance function test was performed with 0.02 mL of 0.4% indigocarmine dye. The function was considered impaired when the interval between the instillation of the dye into the middle ear and its initial appearance on the pharyngeal orifice of the tube exceeded 15 minutes.[1-4]

Another 10 age-matched individuals with traumatic eardrum perforation (n = 10 ears) and no history of previous radiotherapy were enrolled in the study as a comparison sample.

Results. In the longitudinal series, among the 34 NPC patients receiving a complete course of radio-

---

From the Department of Otolaryngology, National Taiwan University, Taipei, Taiwan. Supported by grant NTUH 861543-A58.

CORRESPONDENCE — Yi-Ho Young, MD, Dept of Otolaryngology, National Taiwan University Hospital, 1 Chang-te St, Taipei, Taiwan.

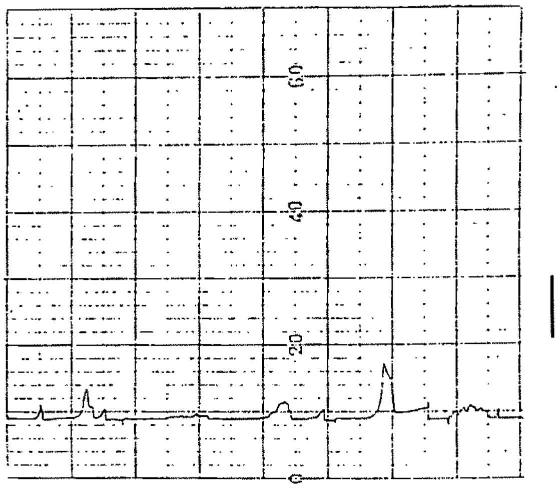


Fig 1. Typical eustachian tube function of nasopharyngeal carcinoma patient with patulous eustachian tube, 10 years postirradiation. Bar — 100 mm H2O.

therapy in 1986, 20 survived 5 years, until 1992, but 6 died later, and 14 survived 10 years, until 1996. Eleven patients received the ETF test again: 8 men and 3 women, with ages ranging from 35 to 71 years, and a mean age of 53 years. The radiation dosage ranged from 70 to 80 Gy, with a mean of 76 Gy. The average body weight was 57 ± 10 kg at 5 years postirradiation and 58 ± 10 kg at 10 years postirradiation, without a significant difference ($p > .05$). In terms of ear symptoms, most patients complained of hearing impairment (73%) and tinnitus (68%), and some patients had aural fullness (23%).

On the passive opening pressure test, 12 (55%) ears were patulous; 9 ears were normal, and only 1 ear was blocked. Figure 1 depicts a typical "ETF-gram" of a patulous tube, demonstrating that the tube was open when a loading pressure less than +100 mm H2O and negative pressure could not be maintained.

The active opening pressure tests (including positive and negative pressure tests) both had 20 (91%) ears with patulous tubes, and 2 ears with a blocked tube. On the clearance function test, 20 (91%) ears had a delayed clearance time, and only 2 ears had a normal clearance function.

Grommeted ears (n = 4) all developed a patulous tube, whereas among the myringotomized ears (n = 18), 8 had a patulous tube, 1 had a blocked tube, and 9 ears had normal tube function.

Except for 2 (9%) ears with chronic otitis media noted by otoscopic findings, the ears had an intact eardrum appearance. The mean hearing levels for bone conduction and air conduction (Fig 2) at 5 years versus 10 years postirradiation revealed no significant difference in hearing deterioration (Student's *t*-test, $p > .01$).

In the control group of 10 subjects, the ages ranged from 35 to 68 years, with a mean of 51. All ears were normal according to the passive opening pressure test. The positive and negative pressure tests both showed 2 (20%) ears with patulous tubes and the rest (8 ears) normal. On the clearance function test, 1 ear had a delayed clearance time, and 9 ears had normal clearance function.

STUDY 2: SONOTUBOMETRY

Patients and Methods. Another 10 NPC long-term (10 years) survivors were randomly selected for sonotubometry (Rion, JK-04, Japan) to confirm the high prevalence of patulous tubes in long-term survivors of NPC.

For sonotubometry, a sound source (7,000 Hz band noise) was applied to the patient's nostril, and a microphone was mounted in the ipsilateral external ear canal for detecting a sound change. When the acous-

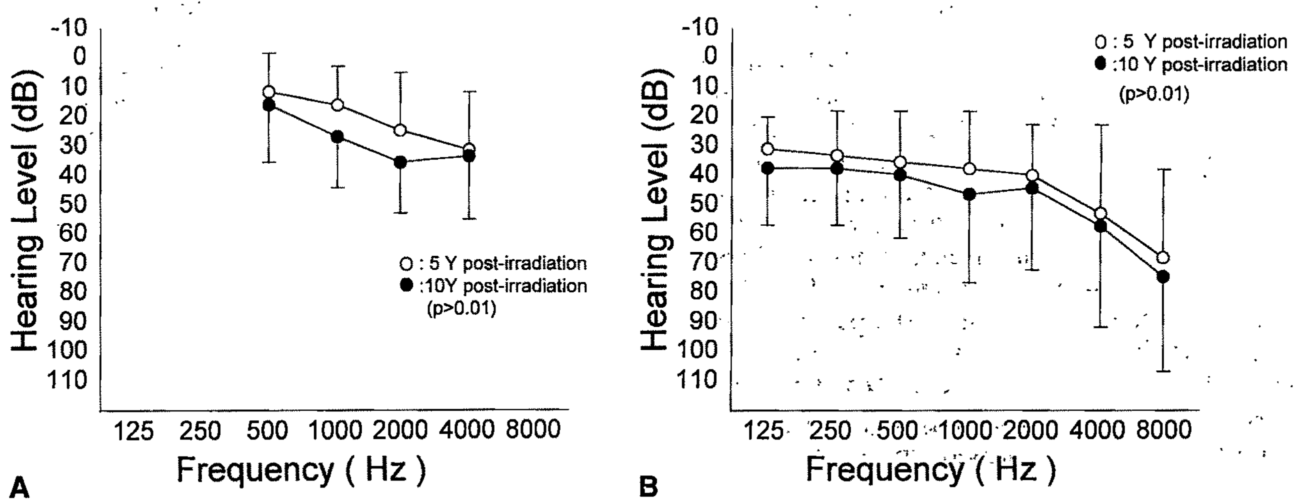


Fig 2. Mean hearing levels for 20 ears, 5 years versus 10 years postirradiation. A) Bone conduction. B) Air conduction.

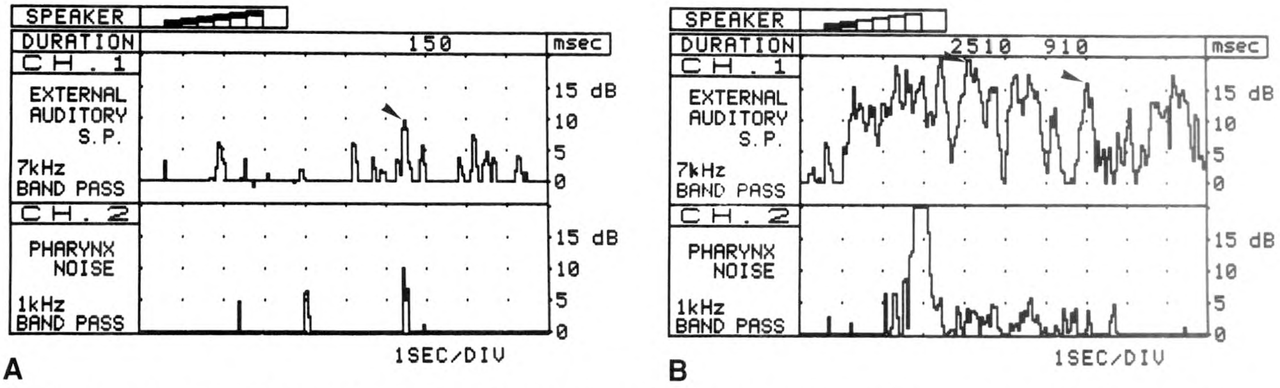


Fig 3. Sonotubometry for nasopharyngeal carcinoma patients, 10 years postirradiation. Channel 1 (upper half) is external ear canal sound pressure level, and channel 2 (lower half) shows pharyngeal noise level. During swallowing, sound pressure change is noted to ascertain duration of tubal opening. Arrowhead — beginning of tubal opening. A) Normal tube. Duration of tubal opening is 150 milliseconds (ms). B) Patulous tube. Durations of 2 instances of tubal opening are 2,510 ms and 910 ms.

tic pressure had reached the external ear canal, the patient was allowed to swallow. When the eustachian tube opened, the sound from the speaker was transmitted through the eustachian tube to the external ear canal, where it caused a rise in sound pressure level and determined the duration of tubal opening.[5]

Results. The 10 patients (5 men and 5 women) ranged in age from 33 to 68 years, with a mean age of 50. The radiation dosage ranged from 70 to 130 Gy (2 patients received irradiation twice), with a mean of 75 Gy. On otoscopic findings, 2 ears had chronic otitis media, whereas the remaining 18 ears all revealed an intact eardrum appearance.

On sonotubometry, 8 tubes were normal (Fig 3A), 10 tubes (50%) were patulous, and 2 ears were blocked. The duration of tubal opening in the patulous tube group ranged from 580 to 3,655 milliseconds (ms), with a mean of 1,227 ms. In contrast, in the normal tube group, the mean duration of tubal opening was 222 ms, for a significant difference ($p < .01$).

Figure 3B reveals the pattern of a patulous tube on sonotubometry. Channel 1 (upper half) indicates the external ear canal sound pressure level, with the durations of tubal opening 2,510 ms and 910 ms. Channel 2 denotes pharyngeal noise, possibly due to velopharyngeal insufficiency. The latter is frequently encountered in long-term survivors of NPC, together with significant hypernasality in their speech.

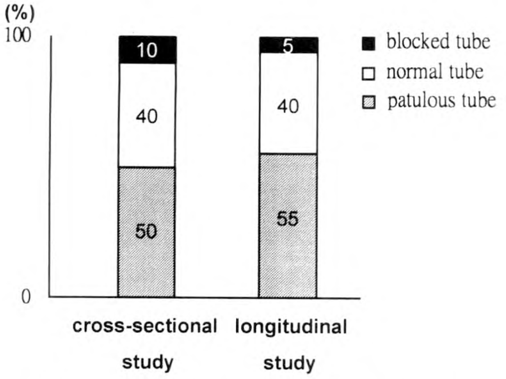


Fig 4. Outcomes of 2 studies (longitudinal versus cross-sectional) of eustachian tube function in long-term survivors of nasopharyngeal carcinoma.

Figure 4 summarizes the most significant findings of the ETF testing and sonotubometry. In the longitudinal study, 55% of the ears had patulous tubes, and in the cross-sectional study, 50% revealed patulous tubes.

DISCUSSION

The eustachian tube is a channel connecting the middle ear cavity and the nasopharynx. It is usually closed, and closure is maintained by the elasticity of its cartilage and mucosal lining and extrinsic factors such as peritubal fat (Ostmann's fatty tissue) and muscles. Any condition that alters the above anatomic structures, eg, radiotherapy, hormones, weight loss, and neurologic disorders, may influence tubal closure and result in a patulous tube.[6,7] A patulous tube is not constantly open; rather, it is insufficiently closed. In previous literature,[6-11] patulous tubes were attributed to factors such as weight loss, drugs, pregnancy, and cranial-facial anomalies. In this paper, confounding factors, specifically weight loss or gain, are ruled out for the development of a patulous tube, since there was no significant difference in body weight at 5 years versus 10 years postirradiation ($p > .05$). Also, the aging process was irrelevant to changes in ETF in the longitudinal sample, because no patulous tube could be detected in an age-matched comparison sample. Therefore, irradiation played the most important role in the occurrence of patulous tubes. In a study of ETF at 5 years postirradiation,[12] 61% were blocked on the passive opening pressure test. On the positive and negative pressure tests, 39% and 44% of tubes were blocked, respectively. Only 11% of ears were patulous on the positive pressure test.[12] In the current study, the prevalence of patulous tubes in NPC patients 10 years after irradiation was 55% on the inflation-deflation test, and 50% on sonotubometry (Fig 4).

The mean radiation dosage for the patulous tube group in study 1 was 77 Gy, and that for the normal tube group was 76 Gy, without any significant difference ($p > .05$). This finding suggests that a patulous tube is unrelated to radiation dosage and instead is related to the interval after irradiation. No patulous tubes could be found in NPC patients 5 years after irradiation, but the prevalence was up to 50% or 55% 10 years after irradiation.

Common symptoms of a patulous tube are aural fullness and autophony, but not tinnitus.[6-11] However, the primary symptom in our NPC patients with a patulous tube was tinnitus, rather than aural fullness, in marked contrast to the conventional patulous tube. The reason for such a discrepancy might be insufficient closure of the tube in the study ears. Besides, patients with conventional patulous tubes generally have normal hearing,[7] whereas our patients with patulous tubes had mixed-type hearing loss. Restated, the patulous tubes in long-term survivors of NPC differed from conventional patulous tubes with respect to symptomatology and audiometry.

The clearance function showed impairment in 91% of the ears 10 years after irradiation, and it was an impairment of both the pumping function of the tensor veli palatini muscle and the mucociliary function of the tube.[13] Among the 21 long-term survivors of NPC, only 4 ears had chronic otitis media; the remaining 38 had an intact eardrum. This finding is quite encouraging.

In addition, comparing the mean hearing levels for bone conduction and air conduction of ears 5 years versus 10 years after radiotherapy (Fig 2) reveals no significant change. This finding suggests that lessening of middle ear complications and subsequently stable hearing status can be found in long-term survivors of NPC. On the basis of the improvement of the middle ear condition and the preservation of hearing status, we can conclude that a patulous tube might positively influence long-term survivors of NPC. A patulous tube can free itself of organic obstruction, and restoration of functional impairment is attributed to subsidence of the inflammatory reaction.

REFERENCES

1. Sato H, Kurata K, Yen Y-H, Honjo I, Young Y-H, Hsieh T. Extension of nasopharyngeal carcinoma and otitis media with effusion. Arch Otolaryngol Head Neck Surg 1988;114:866-7.

2. Young Y-H, Hsieh T. Eustachian tube dysfunction in patients with nasopharyngeal carcinoma, pre- and post-irradiation. Eur Arch Otorhinolaryngol 1992;249:206-8.

3. Young Y-H, Lin KL, Ko J-Y. Otitis media with effusion in patients with nasopharyngeal carcinoma, post-irradiation. Arch Otolaryngol Head Neck Surg 1995;121:765-8.

4. Hsu M-M, Young Y-H, Lin K-L. Eustachian tube function of patients with nasopharyngeal carcinoma. Ann Otol Rhinol Laryngol 1995;104:453-5.

5. Virtanen H. Patulous eustachian tube: diagnostic evaluation by sonotubometry. Acta Otolaryngol (Stockh) 1978;86:401-7.

6. Dyer RK, McElveen JT. The patulous eustachian tube: management options. Otolaryngol Head Neck Surg 1991;105:832-5.

7. Tolley NS, Phelps P. Patulous eustachian tube: a radiological perspective. J Laryngol Otol 1990;104:291-3.

8. O'Connor AF, Shea JJ. Autophony and the patulous eustachian tube. Laryngoscope 1981;91:1427-35.

9. Bluestone CD, Cantekin EI. Management of the patulous eustachian tube. Laryngoscope 1981;91:149-52.

10. Henry DF, DiBartolomeo JR. Patulous eustachian tube identification using tympanometry. J Am Acad Audiol 1993;4:53-7.

11. Flisberg K, Ingelstedt S. Middle-ear mechanics in patulous tube cases. Acta Otolaryngol [Suppl] (Stockh) 1970(suppl 263):18-22.

12. Young Y-H, Cheng P-W, Ko J-Y. A 10-year longitudinal study of tubal function in patients with nasopharyngeal carcinoma after irradiation. Arch Otolaryngol Head Neck Surg 1997;123:945-8.

13. Honjo I, Hayashi M, Ito S, Takahashi H. Pumping and clearance function of the eustachian tube. Am J Otolaryngol 1985;6:241-4.

Ann Otol Rhinol Laryngol 108:1999

SUCCESSFUL TREATMENT OF AN INVASIVE ASPERGILLOSIS OF THE SKULL BASE AND PARANASAL SINUSES WITH LIPOSOMAL AMPHOTERICIN B AND ITRACONAZOLE

MICHAEL STREPPEL, MD
GREGOR BACHMANN, MD
GEORG ARNOLD, MD
MICHAEL DAMM, MD
EBERHARD STENNERT, MD
COLOGNE, GERMANY

Invasive aspergillosis and fulminant aspergillosis are rarities with a high mortality. In the literature there is no patient surviving an extended invasive aspergillosis of the paranasal sinuses and skull base after failure of operative intervention and of postoperative amphotericin B therapy. We report a complete remission of an invasive, partially fulminant aspergillosis. After an incomplete removal of the mycotic mass, we started postoperative drug therapy with amphotericin B. Under this treatment, the mycosis progressed. Additionally, the patient developed severe side effects, so that the treatment was interrupted. At this moment, we started a combined antimycotic drug therapy with liposomal amphotericin B and itraconazole. Within 10 weeks, clinically and radiologically, there was complete remission. The patient died 63 weeks after this treatment, due to a fulminant bacterial pneumonia. Postmortem histologic examination showed no aspergillosis in the skull base, paranasal sinuses, or lung.

KEY WORDS — drug therapy, fulminant aspergillosis, itraconazole, liposomal amphotericin B, paranasal sinus, sinusitis complications, skull base.

INTRODUCTION

Aspergillosis belongs to the category of systemic mycoses. The agent is a ubiquitous and facultative pathogen: usually, *Aspergillus fumigatus* or *Aspergillus flavus*; more rarely, *Aspergillus niger* or *Aspergillus terreus*. The lungs, skin, and paranasal sinuses are the preferred localities. The following clinical and pathologic subgroups are distinguished[1-3]: 1) saprophytic forms without infiltration or destruction of the surrounding tissue (allergic aspergillus sinusitis, aspergilloma) and 2) invasive forms with destruction of the tissue (invasive aspergillosis, fulminant aspergillosis with a severe course).

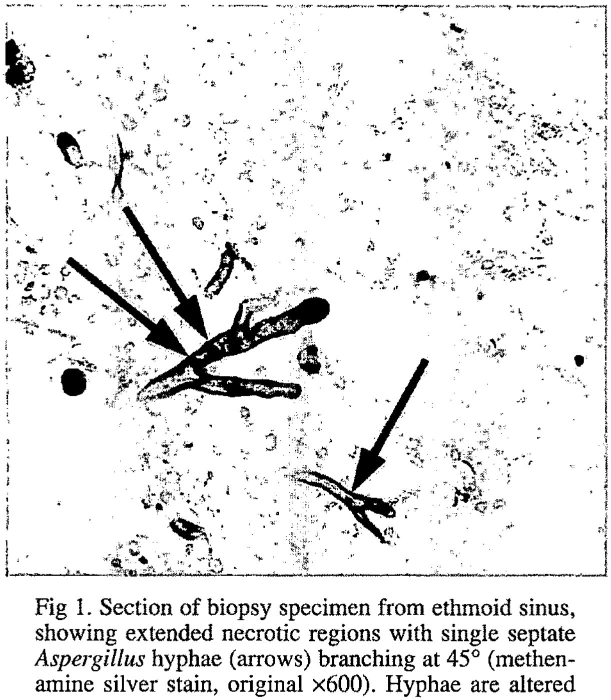


Fig 1. Section of biopsy specimen from ethmoid sinus, showing extended necrotic regions with single septate *Aspergillus* hyphae (arrows) branching at 45° (methenamine silver stain, original ×600). Hyphae are altered regressively. Additionally, some granulomatous reactions were detected (not shown here).

The invasive and, in particular, the fulminant forms are rarities with a very high mortality. They were first described by Wright[4] in 1927. Since then, they have clearly increased,[5,6] due to the fact that predisposing factors leading to immunodeficiency are increasing[7] (see Table).

We report the case of a 50-year-old woman with an invasive and fulminant aspergillosis of the paranasal sinuses and the skull base successfully treated with liposomal amphotericin B and itraconazole.

FACTORS PREDISPOSING TO IMMUNODEFICIENCY
Infectious immunodeficiency (acquired immunodeficiency syndrome, etc)
Congenital immunodeficiency (Wiskott-Aldrich syndrome, etc)
Drug-induced immunodeficiency (chemotherapy, cortisone therapy, etc)
Cancer diseases
Diabetes mellitus

From the Department of Otolaryngology–Head and Neck Surgery (Streppel, Bachmann, Damm, Stennert), and the Institute of Pathology (Arnold), University of Cologne, Cologne, Germany.

CORRESPONDENCE — Michael Streppel, MD, Klinik und Poliklinik für Hals-Nasen-Ohrenheilkunde der Universität Köln, Josef Stelzmann Strasse 9, D-50924 Köln, Germany.

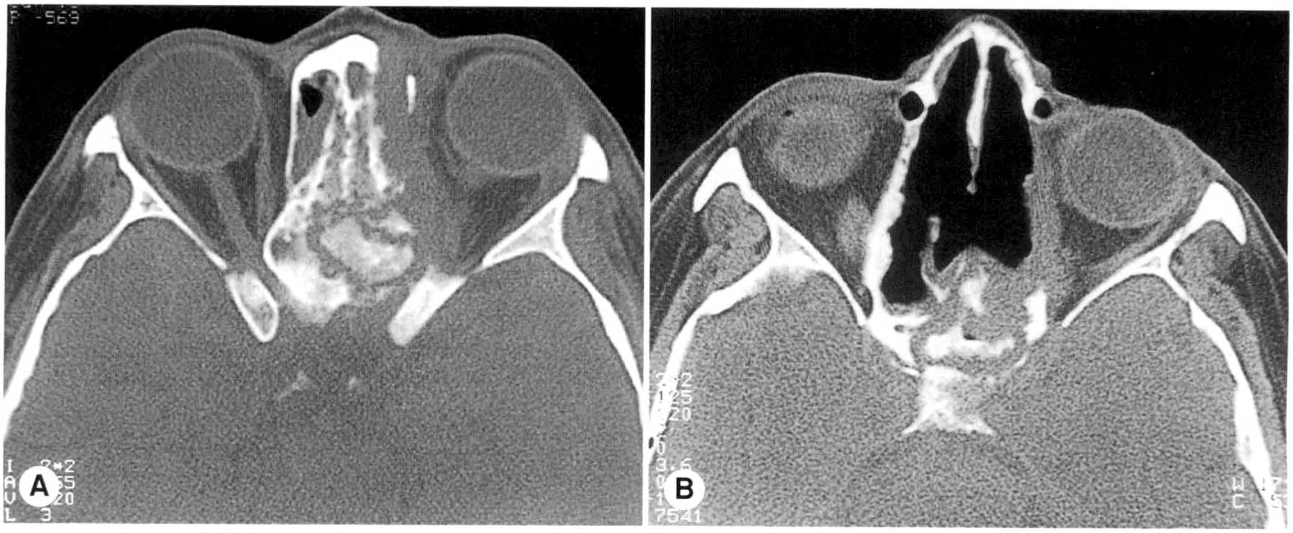


Fig 2. Computed tomography scans. A) Day 127. Destruction of left anterior skull base and of ethmoid cells. Additionally, invasion and destruction of clivus, left frontal sinus, and zygomatic bone and alteration of dura in this region. No infiltration of intracerebral structures. B) Day 187. Obviously marked improvement of opacity in frontal skull base. Good ventilation in ethmoid region. No invasion into left orbit. Persistent postinflammatory alterations of clivus.

CASE REPORT

In April 1994, a 50-year-old woman presented herself clinically with acute sinusitis and periorbital edema. We performed an endoscopic endonasal and extranasal paranasal sinus operation. A gray-yellow necrotic mass was present in the left ethmoid sinus, extending to the frontal sinus and the orbit. Histologic examination of tissue showed infiltrating *Aspergillus* hyphae as seen in the biopsy specimen (Fig 1). Therefore, postoperative intravenous drug therapy with amphotericin B (initially 0.5 mg/kg per day, increased to 1.0 mg/kg per day) was started. On day 44, the patient's creatinine level had increased to 45 mg/L, and her hemoglobin level had decreased to 79 g/L. Due to these side effects, the treatment had to be discontinued. As there was endoscopic evidence of residual mycosis (a gray, necrotic mass in the left ethmoid sinus), an endonasal and extranasal revision was performed on day 83. At this stage, a marked infiltration of the zygomatic bone, sphenoid bone, ethmoidal cells, and frontal sinuses, as well as the whole left anterior skull base, was obvious (Fig 2A). Once more, histologic examination detected invasive *Aspergillus* hyphae (similar to those in Fig 1). Complete surgical removal was not possible. Immediately, we commenced intravenous therapy with liposomal amphotericin B (up to 3 mg/kg per day) and oral itraconazole (200 mg 4 times per day). Computed tomography showed continuous improvement of the inflammatory alterations (Fig 2B). The patient was discharged on day 184 on maintenance therapy of oral itraconazole 100 mg 3 times per day. The patient died on day 635 because of a fulminant bacterial pneumonia. A postmortem histologic examination did not show any signs of a residual mycosis of the paranasal sinuses or skull base.

DISCUSSION

Mortality due to fulminant aspergillosis is high. Antoine et al[5] gave an overview of the literature, quoting a mortality of 75%. Additionally, involvement of the orbita makes the prognosis worse.

Until today, the method of choice in cases of invasive or, particularly, fulminant aspergillosis of the paranasal sinuses or skull base was primary and complete surgical removal of affected structures.[8,9] In cases of incomplete removal, a postoperative antimycotic drug treatment should follow the surgical intervention. The discussion continues as to whether or not postoperative drug therapy is effective.[3,5,10] All cases reported with incomplete surgical removal and progression under postoperative drug therapy were lethal. Here is the key point for the presented case. After incomplete removal and progression under postoperative amphotericin B therapy, there was a definite cure under combination therapy with liposomal amphotericin B and itraconazole. The postmortem histologic examination proved the complete elimination of the aspergillosis in the paranasal sinuses and skull base.

Amphotericin B has a high toxicity that is decreased by liposomal capsulation.[11] By this, it is possible to give higher serum levels with higher drug levels in the tissue altered by the mycosis. Itraconazole is a triazole drug with few side effects. It has a low serum but a high tissue concentration. It is unknown whether or not itraconazole and liposomal amphotericin B are acting in a synergistic way.

A question arises as to the method of treatment of invasive and, particularly, fulminant aspergillosis. Could the presented antimycotic drug combination replace a high-risk surgical intervention at the skull base? Or is the combination of surgical and drug treatment still the method of choice? Further data on these substances need to be collected.

REFERENCES

1. Hora JF, Houston FS. Primary aspergillosis of the paranasal sinuses and associated areas. Laryngoscope 1965;75:768-73.
2. Katzenstein A, Sale S, Greenberger P. Allergic *Aspergillus* sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol 1983;72:89-93.
3. McGill TJ, Simpson G, Healy GB. Fulminant aspergillosis of the nose and paranasal sinuses: a new clinical entity. Laryngoscope 1980;90:748-54.
4. Wright RE. Two cases of granuloma invading orbit due to aspergillosis. Br J Ophthalmol 1927;11:545-59.
5. Antoine GA, Gates RH, Park AO. Invasive aspergillosis in a patient with aplastic anemia receiving amphotericin B. Head Neck Surg 1988;10:199-203.
6. Landoy Z, Coleman R, Shedd D. Aspergillosis of the nose and paranasal sinuses in neutropenic patients at an oncology center. Head Neck Surg 1985;8:83-90.
7. Vanderstock L, Vander Eecken P, Vermeersch H, Cuvelier C. Aspergillose van de maxillaire sinus. Acta Otorhinolaryngol Belg 1981;35:148-53.
8. De Foer C, Fossion E, Vaillant JM. Sinus aspergillosis. J Craniomaxillofac Surg 1990;18:33-40.
9. Chang T, Teng MMH, Wang SF, Li WY, Cheng CC, Lirng JF. Aspergillosis of the paranasal sinuses. Neuroradiology 1992; 35:520-3.
10. Romett JL, Newman RK. Aspergillosis of the nose and the paranasal sinuses. Laryngoscope 1982;92:764-6.
11. Janoff AS, Boni LT, Popescu MC. Unusual lipid structures selectively reduce the toxicity of amphotericin B. Proc Natl Acad Sci USA 1988;85:6122-6.

≈

EAR SURGERY

The 34th Annual Postgraduate Course in Ear Surgery will be held April 5-10, 1999, in Nijmegen, the Netherlands. For information, contact Prof.dr. P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax +31 24 3540251; e-mail J.Cornelisse@kno.azn.nl.

Ann Otol Rhinol Laryngol 108:1999

VASOMOTOR RHINITIS FOLLOWING TRAUMA TO THE NOSE

SAMUEL SEGAL, MD
NATHAN SHLAMKOVITCH, MD
EPHRAIM EVIATAR, MD
LEONARD BERENHOLZ, MD
SHLOMO SARFATY, MD
ALEXANDER KESSLER, MD
ZERIFIN, ISRAEL

Complaints of nasal obstruction following nasal trauma without any deformation have been noticed by rhinologists for many years. However, neither an epidemiologic nor a pathophysiologic connection has ever been established. The complaints and physical examination findings of these patients resemble those of vasomotor rhinitis. Only very few articles suggesting nasal trauma as a possible cause for vasomotor rhinitis have ever been published. We present a retrospective study that found 87 of 802 patients to suffer from vasomotor rhinitis following nasal trauma. No other factors known to cause vasomotor rhinitis were present in these patients. None had any previous nasal problems. We therefore suggest that nasal trauma was the causative factor in their vasomotor rhinitis.

KEY WORDS — nasal trauma, vasomotor rhinitis.

INTRODUCTION

Vasomotor rhinitis is clinically characterized by nasal obstruction, increased secretion, and an impaired sense of smell. It is a noninfectious, nonallergic entity, experimentally suggested to be the result of autonomic imbalance with a relative dominance of the parasympathetic nervous system in the nasal mucosa.[1,2]

The cause of vasomotor rhinitis is manifold and basically unknown. Different factors such as emotional disturbance, endocrine hormones, and physical agents are usually thought to be predisposing factors.[3] From our clinical observations, we found trauma to the nose to be an additional potential causative factor of vasomotor rhinitis. Although it is not rare to find the disorder as a result of surgical or accidental trauma to the nose, there are apparently only a few reports on this issue.[4,5] The few reports suggest a possible connection between the complaints and physical findings and previous nasal trauma. Daniel, in his book *Aesthetic Plastic Surgery–Rhinoplasty*, states, "A little recognized complication of nasal trauma is rhinitis. Rhinitis may settle in time (ie, several months), but persistent discharge may be treated with steroids or anticholinergic nasal sprays. Refractory rhinitis usually requires turbinate surgery."[6(p655)] Yet, no known study significantly proving a connection between these 2 factors has ever been published.

The purpose of this study is to evaluate the role of nasal trauma in inducing vasomotor rhinitis and to discuss the possible pathogenesis of this disorder.

MATERIALS AND METHODS

Eighty-seven patients out of 1,291 disabled military veterans of the Israeli Defense Forces who suffered from nasal trauma were studied between 1977 and 1995 and met the following criteria:

1. Nasal symptoms characteristic of vasomotor rhinitis.
2. Onset of symptoms from 4 months to 1 year following nasal trauma.
3. No history of nasal disorder prior to the trauma.
4. No history of allergy, IgE levels of less than 50 mg/mL, and a negative skin test.
5. No signs of sinusitis on radiography.
6. No structural deformity of the nose, face, or head.
7. Since 1989, anterior rhinomanometry was used to evaluate patients who sustained nasal trauma in order to establish a rhinomanometry baseline. Rhinomanometry evaluation was performed, followed by a second evaluation after application of local nasal vasoconstrictors. Only those patients with a marked decrease of airflow caused by local vasoconstriction were included in our study group.

Three hundred twelve patients who suffered from acoustic trauma without any nasal trauma were selected as a control group. All the patients of the control group met the standards given for the study group. All the patients, study and control groups,

---

From the Department of Otolaryngology, Assaf Harofeh Medical Center, Sackler School of Medicine, Tel-Aviv University, Zerifin, Israel.
CORRESPONDENCE — Samuel Segal, MD, Dept of Otolaryngology, Assaf Harofeh Medical Center, Zerifin, Israel 70300.

TABLE 1. PHYSICAL FINDINGS IN SUBJECTS WITH VASOMOTOR RHINITIS

	Study Group		*Control Group*	
	No.	*%*	*No.*	*%*
Nasal breathing difficulty	87	100.0	11	100.0
Hypertrophy of nasal mucosa	87	100.0	9	81.8
Redness of nasal mucosa	53	60.9	5	45.5
Nasal secretions	40	46.0	6	54.5

were first examined within a few days of the injury. A detailed examination was made, including a detailed medical questionnaire completed by the patients. The major role of the questionnaire was to exclude the presence of any previous nasal obstruction in order to limit any bias resulting from the patient's wish for secondary gain.

The patients were seen a few weeks after their injury and were followed up between 4 months and 2 years postinjury. All the patients who presented with signs of allergic rhinitis, according to the above criteria, were excluded from the study.

The role of the control group was to exclude any other factors that might have influenced the physical conditions that cause vasomotor rhinitis (eg, emotional disturbances following the trauma, secondary gain, etc).

RESULTS

Eighty-seven of the 1,291 patients who underwent nasal trauma showed symptoms resembling vasomotor rhinitis. Eighty-two patients were excluded from the study group for various reasons. Four hundred seven patients did not meet the meticulous standards mentioned above (in Materials and Methods). The remaining 715 patients remained asymptomatic.

Three hundred twelve patients who suffered from acoustic trauma and met the standards were used as a control group. Eleven patients had symptoms of rhinitis. Their complaints and symptoms included 1 or a combination of the following. All complained of nasal breathing difficulties. Nine had nasal mucosal hypertrophy. One patient without mucosal hypertrophy suffered from increased nasal secretions, and the other patient from secretions and redness of the nasal mucosa. Some of the patients with hypertrophy of the nasal mucosa also had increased secretions from the nose and/or redness of the nasal mucosa.

Table 1 summarizes the physical findings of the study group compared to the controls. Among the patients who complained of nasal breathing difficulty within the study group, hypertrophy of the nasal mucosa was found in all the patients (100%), while redness was found only in 53 (60.9%) and nasal secretions in 40 (46%) of the individuals. It is to be emphasized that some patients had only 1 symptom, whereas others appeared to suffer from a combination of symptoms. In order to simplify the data, the findings in Table 1 are noted separately. Data were subjected to χ^2 analysis and were found to be statistically significant (Table 2). According to our findings the relative risk (odds ratio) of developing vasomotor rhinitis was 3.330 (99% confidence interval, 1.409 to 8.111) in patients who had suffered nasal trauma when compared to controls.

TABLE 2. RATE OF OCCURRENCE OF VASOMOTOR RHINITIS

	Study Group	*Control Group*
No evidence of disease	715	301
Vasomotor rhinitis	87	11

$p < .0001$.

Odds ratio is 3.330 (99% confidence interval is 1.409 to 8.111).

DISCUSSION

The nasal vasomotor reaction is controlled by the highly complex autonomic nervous system. The main parasympathetic supply to the nasal mucosa is by the vidian nerve.[7] The preganglionic fibers synapse in the sphenopalatine ganglion, and the postganglionic cholinergic fibers are mainly distributed over the arteries, arterioles, and nasal glands. The sympathetic nerve supply to the nose is supplied to the vascular system predominately, and very sparsely to the glands. Studies conducted by Malcomson[8] on the autonomic nervous system of the nose revealed that stimulation of the parasympathetic nerves produced vasodilation and increased secretion, whereas sympathetic nerve stimulation produced intense vasoconstriction. Any vasodilator substance can cause the nasal vasomotor reaction to occur; however, the most important and powerful is acetylcholine, which is constantly released at the parasympathetic fiber nerve endings. Acetylcholine is rapidly destroyed by acetylcholinesterase. The balance between the rates of acetylcholine production and destruction is controlled by the hypothalamus.

Vasomotor rhinitis results primarily from autonomic dysfunction. The parasympathetic prevalence may be induced by central or peripheral stimulation. Prolonged emotional states, fatigue, and pain may result in central hypothalamic stimulation that causes a parasympathetic overflow producing the vasomotor reaction in the nose.[3] The other possible mechanism is by stimulation of the main parasympathetic ganglion: the sphenopalatine. Krajina and Poljak[9] suggest vasomotor rhinitis to be the result of stimulation of the ganglion due to its unique location near the nose, exposing it to external stimuli. Bleeding into the ganglion is such a possible stimulus. There is the possibility of a synergistic action of both mechanisms: direct stimulation of the mucosal nerve fibers and the ganglion as well. Recent pharmacologic studies have revealed that there is a third group of mediators, other than the neurotransmitters norepinephrine and acetylcholine. These have been identified as the neuropeptides, the most important one for the nasal mucosa being substance P (SP). This is one of the mediators of sensory and vagal afferent neurons that are known as unmyelinated C fibers.[10,11] The pharmacologic effects of SP include vasodilation, plasma extravasation (neurogenic edema), hypersecretion, and smooth muscle contraction. The edema is enhanced by histamine release by mast cells triggered by SP liberation.[12,13]

Nasal trauma resulting from rhinoplasties, septoplasties, and nasal fractures was found to be a potential etiologic factor in producing vasomotor rhinitis. Although theoretically based, and in spite of our clinical impression that nasal trauma is a predisposing factor for developing symptoms resembling rhinitis, we did not find in a review of the literature any articles discussing this as an etiologic factor. We decided to use the data we collected while treating military veterans. We isolated a study group whose only injury was nasal trauma, and compared them to an appropriate control group.

After eliminating factors that might affect the results, we were left with individuals who suffered from nasal trauma and had no other factors that might influence the results, such as previous history of nasal obstruction, nasal structural deformities, high levels of serum IgE, and abnormal sinus radiographs. We compared our study group to controls who were suffering from acoustic trauma. They all met the same criteria and had no previous history of nasal disorders. The data were subjected to χ^2 analysis and were found to be statistically significant, indicating a much higher rate of rhinitis in individuals who had undergone nasal trauma compared to those who had not.

Our study indicates that in addition to the abovementioned factors, blunt nasal trauma can also cause vasomotor rhinitis.[6] We believe that in these cases, vasomotor reaction is the result of a peripheral localized parasympathetic overactivity that may be induced by 2 mechanisms. One is through direct stimulation of the parasympathetic nerve endings in the nasal mucosa, which is the result of the anatomic changes in the nasal tissues produced by the trauma. Beekhuis,[4] who reports vasomotor rhinitis in 10% of all his rhinoplasty patients, believes that it is the result of autonomic changes, especially in the turbinates. We believe that along with the neurotransmitters, the neuropeptides play a second important role in provoking posttraumatic vasomotor rhinitis through local reflexes. In our study, we point out previous nasal trauma as one of the possible causes of vasomotor rhinitis, as all other known factors were excluded.

We conclude that vasomotor rhinitis is significantly higher among patients who suffered previous nasal trauma compared to patients who did not. The statistically significant results show clearly that nasal trauma is a possible cause of vasomotor rhinitis. Further investigation should be performed in order to establish the pathophysiologic process resulting in vasomotor rhinitis caused by nasal trauma.

REFERENCES

1. Axelsson A. Vasomotor rhinitis treated with Lunerin (Draco): a new sympathomimetic antihistaminic preparation. Acta Allergol 1972;27:186-94.
2. Whicker JH, Neel HB, Kern EB, Reynolds HY. A model for experimental vasomotor rhinitis. Laryngoscope 1973;83: 915-22.
3. Taylor M. The nasal vasomotor reaction. Otolaryngol Clin North Am 1973;6:645-54.
4. Beekhuis GJ. Nasal obstruction after rhinoplasty: etiology and techniques for correction. Laryngoscope 1976;86:540-8.
5. Roos RL. Obstruction nasal et les rhinites aperiodiques en Alsace. J Med Strasbourg 1973;4:135-40.
6. Daniel RK. Aesthetic plastic surgery–rhinoplasty. Boston, Mass: Little, Brown, 1993:655.
7. Krajina Z. Vidian neurectomy in vasomotor rhinitis. Acta Otolaryngol (Stockh) 1973;76:366-71.
8. Malcomson KG. The vasomotor activities of the nasal mucous membrane. J Laryngol Otol 1959;73:73-98.
9. Krajina Z, Poljak Z. Relationship between the vegetative innervation and the sensibility of the nasal mucosa. Acta Otolaryngol (Stockh) 1975;79:172-5.
10. Gamse F. Physiologie und Pathophysiologie der Substanz P. Arzneimittelforschung 1984;34:1074-9.
11. Gamse R, Holzer P, Lembeck F. Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br J Pharmacol 1980;68:207-13.
12. Wolf G, Loidolt D, Saria A. Anderungen des nasalen Volumsstromes nach lokaler Applikation des Neuropeptides Substanz P und von Capsaicin. Laryngol Rhinol Otol (Stuttg) 1987; 66:412-5.
13. Pernow B. Substance P. Pharmacol Rev 1983;35:85-141.

IMAGING CASE STUDY OF THE MONTH

MULTIPLE MYELOMA PRESENTING AS PROPTOSIS

CHRISTOPHER RYDER, MD
CORNING, NEW YORK

ROBERT M. NACLERIO, MD
CHICAGO, ILLINOIS

Proptosis, as a presenting complaint, occurs infrequently in otolaryngology. Even more rarely does an extramedullary plasmacytoma as a manifestation of multiple myeloma involve the orbit. We present such a case.

CASE REPORT

A 64-year-old black woman was referred for diagnostic evaluation. She had a 6-week history of headache and blurred vision of her left eye such that she could not count fingers held in front of her face. She denied diplopia, trauma, nasal congestion, and nasal drainage. Her sense of smell was intact. Except for a penicillin allergy, her medical history was unremarkable.

On physical examination, she had mild left proptosis and intact extraocular motions. There was no cervical adenopathy. A small amount of adenoid tissue and a split left uncinate were seen on fiberoptic nasopharyngoscopy.

Magnetic resonance imaging (MRI) and computed tomography (Figs 1 and 2) performed at an outside hospital had shown a soft tissue mass in the left sphenoid sinus, left superior orbital fissure, and left orbital apex, with bone erosion of the lateral wall of the sphenoid sinus at the superior orbital fissure.

The patient was taken to the operating room for an endoscopic biopsy of the sphenoid sinus, which showed an abnormal respiratory mucosa with focal chronic inflammation and necrosis. She was treated with erythromycin for 3 weeks. Her headaches decreased in severity, but her vision was unchanged. Repeat MRI showed no improvement in the appearance of the soft tissue. A left endoscopic medial orbital wall decompression and sphenoid sinusotomy were performed, with biopsies of the left sphenoid sinus and orbital mass. Friable tissue was found in the sphenoid sinus and in the posterior medial orbit. A histologic section from the orbital biopsy specimen was consistent with an extramedullary plasmacytoma of the orbit. The patient was subsequently found by a bone marrow biopsy to have multiple myeloma.

DISCUSSION

Extramedullary plasmacytomas, either as solitary

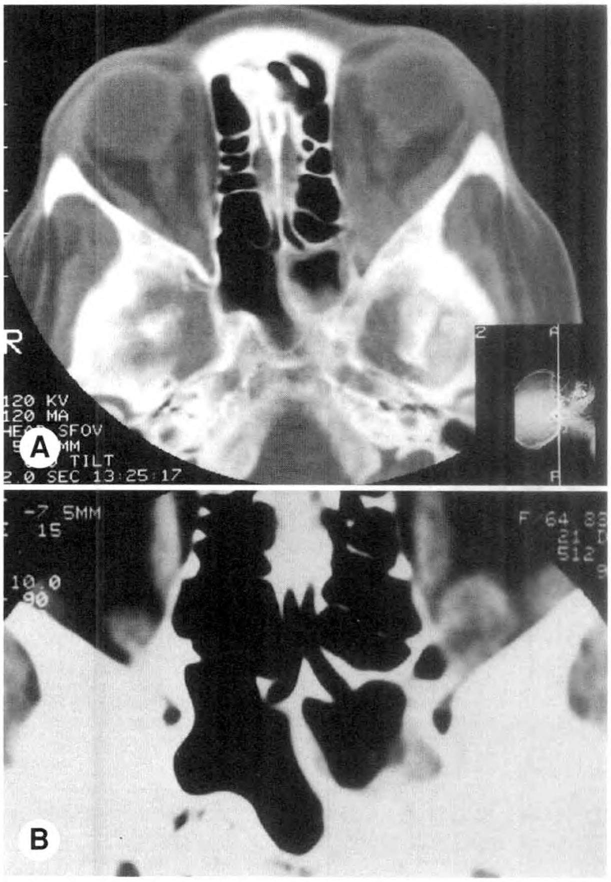


Fig 1. Axial computed tomography scan with A) bone windows and B) soft tissue windows through orbital apex, demonstrating soft tissue mass in left sphenoid sinus, left superior orbital fissure, and left orbital apex, with bone erosion of lateral wall of sphenoid sinus at superior orbital fissure. Proptosis of eye is also noted.

From the Department of Otolaryngology–Head and Neck Surgery, University of Chicago, Chicago, Illinois. Dr Ryder is currently in private practice in Corning, New York.

CORRESPONDENCE — Robert M. Naclerio, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Chicago, 5841 S Maryland Ave/MC 1035, Chicago, IL 60637.

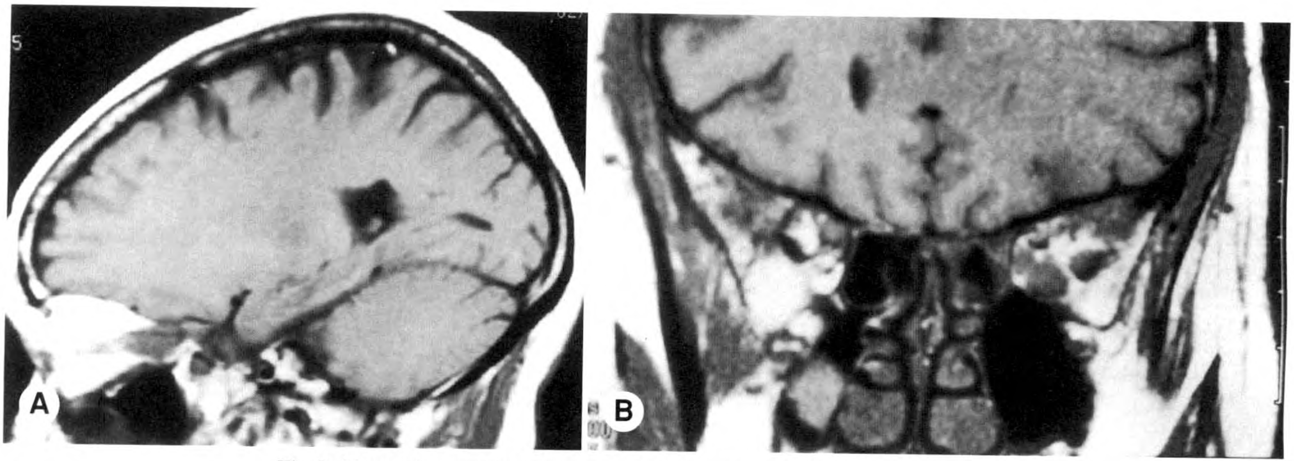


Fig 2. Magnetic resonance images of orbital mass. A) Sagittal. B) Coronal.

lesions or as manifestations of multiple myeloma, rarely involve the orbit. Only 13 cases of solitary extramedullary plasmacytomas were known as of 1995.[1] Thirty-eight cases of orbital extramedullary plasmacytomas associated with multiple myeloma had been reported by 1972.[2] Involvement of the conjunctiva, cornea, uvea, and retina occurs most commonly. Further, in a compilation of 4 series of orbital tumors,[3] only 4 of nearly 2,000 such tumors were plasmacytomas. Proptosis is the most common initial complaint. Other symptoms include vision loss, ptosis, epiphora, diplopia, and conjunctival congestion. Pain is rare. Plasmacytomas are seldom suspected prior to tissue biopsy, unless the patient has a known preexisting multiple myeloma.

Multiple myeloma, a plasma cell dyscrasia characterized by overproduction of 1 distinct immunoglobulin or a fragment of an immunoglobulin molecule, arises from the transformation of a pluripotent stem cell. The specific immunoglobulin or fragment is identified by immunoelectrophoresis. Rarely is there polyclonal overproduction, although when it occurs, it often represents a benign process. Proliferation of myeloma cells depends on cytokines, notably interleukin-6. The cytokines also activate osteoclasts, leading to characteristic osteolytic lesions.

Henry Bence-Jones, in 1847, described the abnormal urine protein commonly associated with multiple myeloma that now bears his name. These proteins represent incomplete light chains. The name multiple myeloma was coined in 1873 by Rutizsky for a patient with multiple bone tumors and Bence-Jones proteinuria.[4]

The incidence of multiple myeloma is 3:100,000. Blacks are affected more frequently than whites, and there is an equal male and female prevalence. The median age at diagnosis is 60 years.

In a typical case of multiple myeloma, bone marrow biopsy shows more than 10% of plasma cells arranged in sheets and at multiple levels of maturity. The vertebrae are the most commonly involved (66%), followed by the ribs (44%), skull (41%), and pelvis (28%). More than 90% of the lesions are in red bone marrow. Anemia, hypercalcemia, recurrent infections, and chronic renal insufficiency are other manifestations of multiple myeloma.

Solitary osseous plasmacytomas were first reported in 1897. These are lytic bone lesions in patients with otherwise normal findings on skeletal survey and bone marrow biopsy, and a biopsy-proven plasma cell tumor. Men and women are affected nearly equally, and the median age at diagnosis is 50 years. Solitary osseous plasmacytomas appear to be early manifestations of multiple myeloma, with dissemination within 3 years in the majority of cases.[5,6]

Extramedullary plasmacytomas, first reported in 1905, are soft tissue plasma cell tumors. Solitary extramedullary plasmacytomas have no evidence of bone marrow disease, and findings on skeletal radiographs are normal aside from bone erosion adjacent to the plasmacytoma.[6] More than 75% are located in the subepithelial tissue of the upper airway or paranasal sinuses. Men are affected 3 to 5 times more frequently than are women, and the median age at diagnosis is 55 to 60 years. Spread seems to be through the lymphatic channels, with up to a 30% recurrence rate after treatment. However, dissemination is much less common than with solitary osseous plasmacytomas. Solitary extramedullary plasmacytomas are considered to be a separate disease process, whereas solitary osseous plasmacytomas are probably in a continuum toward multiple myeloma.[5,6]

It is important to distinguish multiple myeloma from solitary extramedullary plasmacytoma because of the difference in the prognosis. If untreated, patients with multiple myeloma rarely survive for 1 year. Even with chemotherapy, which leads to remission in 75% of multiple myeloma patients, the median survival is only 3 years. With solitary extramedullary plasmacytomas, the mean survival is 8.3 years.[7] Histologically, extramedullary plasmacytoma is indistinguishable from well-differentiated multiple myeloma. Therefore, a skeletal survey, bone marrow biopsy, and immunoelectrophoresis must be obtained so that multiple myeloma can be ruled out.

Well-differentiated plasma cell tumors progress more slowly to disseminated disease than do poorly differentiated plasma cell tumors. In Hokamp and Grundmann's[8] retrospective review of 119 cases of plasmacytoma with bone involvement, 13% of cases of well-differentiated plasmacytoma and 87% of cases of poorly differentiated plasmacytoma had 2 or more disseminated osteolytic lesions. Of the 28 cases of plasmacytoma without osteolytic lesions, 64% were well differentiated, 32% were moderately differentiated, and only 4% were poorly differentiated.

The initial treatment of solitary extramedullary plasmacytomas is radiotherapy. Surgery and chemotherapy are reserved for recurrent or persistent disease.[7] Chemotherapy is the treatment of choice for multiple myeloma, whereas radiotherapy may be useful for localized lesions.

The differential diagnosis of proptosis includes traumatic injuries, metabolic disorders, vascular lesions, inflammatory lesions, complications of sinus disease (inflammatory or neoplastic), and orbital neoplasms. The most common cause of proptosis in adults is Graves' ophthalmopathy. Orbital pseudotumors are characterized by a solitary mass, often involving the lacrimal gland, and diffuse enlargement of 1 or more extraocular muscles.[9] Benign inflammatory processes include sarcoidosis, Wegener's granulomatosis, Lyme disease, desmoid cysts, pleomorphic adenomas of the lacrimal gland, histiocytosis, and cavernous hemangioma, which is the most common benign orbital tumor. Malignant neoplasms include optic nerve tumors (usually meningiomas), lymphomas, leukemias, gliomas, metastases, lacrimal gland malignant tumors, rhabdomyosarcomas, and contiguous malignancies from the globe or skin.

This patient's presentation (proptosis and vision loss from the orbital plasmacytoma) occurred in 23 of Rodman and Font's[2] 30 cases of orbital plasmacytoma and multiple myeloma.

REFERENCES

1. Aboud N, Sullivan T, Whitehead K. Primary extramedullary plasmacytoma of the orbit. Aust N Z J Ophthalmol 1995; 23:235-9.

2. Rodman HI, Font RL. Orbital involvement in multiple myeloma. Arch Ophthalmol 1972;87:30-5.

3. Mewis-Levin L, Garcia CA, Olson JD. Plasma cell myeloma of the orbit. Ann Ophthalmol 1981;13:477-81.

4. Knapp AJ, Gartner S, Henkind P. Multiple myeloma and its ocular manifestations. Surv Ophthalmol 1987;5:343-51.

5. Wiltshaw E. The natural history of extramedullary plasmacytoma and its relationship to solitary myeloma of bone and myelomatosis. Medicine 1976;55:217-38.

6. Knowling MA, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. J Clin Oncol 1983;1:255-62.

7. DeSmet M, Rootman J. Orbital manifestations of plasmacytic lymphoproliferations. Ophthalmology 1987;94:995-1003.

8. Hokamp HG, Grundmann E. Histological grading and clinical staging of plasmacytoma. J Cancer Res Clin Oncol 1983;105:197-8.

9. Char DH. Symposium on ocular tumors. Part II. Management of orbital tumors. Mayo Clin Proc 1993;68:1081-96.

Ann Otol Rhinol Laryngol 108:1999

CLINICOPATHOLOGICAL CONSULTATION

LARYNGEAL PATHOLOGY IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME: DIAGNOSTIC AND THERAPEUTIC DILEMMAS

THOMAS A. TAMI, MD
CINCINNATI, OHIO

ALFIO FERLITO, MD
UDINE, ITALY

ALESSANDRA RINALDO, MD
UDINE, ITALY

KELVIN C. LEE, MD
SAN FRANCISCO, CALIFORNIA

BHUVANESH SINGH, MD
BROOKLYN, NEW YORK

The acquired immunodeficiency syndrome has produced a growing population of patients who, because of their associated immune system compromise, are prone to opportunistic infections and neoplastic diseases. The larynx, with its relatively inaccessible yet critical anatomic location, is a site in which these processes can produce clinical dilemmas, with respect to diagnosis as well as to therapy. By presenting 4 cases involving unusual laryngeal problems in patients infected with the human immunodeficiency virus (HIV), we emphasize these inherent diagnostic and therapeutic problems. Otolaryngologists must be familiar with the many diagnostic possibilities and therapeutic alternatives when HIV-infected patients present with laryngeal complaints.

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) epidemic has had a major impact on every medical specialty. As the worldwide prevalence of this infection continues to increase, diseases that were previously rare conditions have crept back into the differential diagnosis and are encountered with increasing frequency. In no anatomic region is this more apparent than in the head and neck, and specifically in the larynx. When patients infected with the human immunodeficiency virus (HIV) present with laryngeal symptoms, the differential diagnosis must now include unusual and aggressive opportunistic infections, as well as various neoplastic processes. In many cases, the diagnosis is difficult to establish preoperatively and requires early biopsy to allow appropriate therapy to be initiated. In some cases, what might otherwise be an indolent process can rapidly transform into a fulminant, life-threatening condition.

The following cases provide a glimpse into the variety of pathologic problems that have been encountered in the larynx in HIV-infected patients. Only by developing a differential diagnosis that includes these and other unusual laryngeal conditions will an accurate diagnosis be established in these cases.

CASE REPORTS

CASE 1

A 46-year-old homosexual man was referred to an otolaryngology department in late February 1996 for evaluation of dysphagia, severe throat pain, and a 2-month history of a 2.5-kg weight loss. Significant past medical history included hepatitis A (in 1976), psoriasis (1979), herpes zoster (1986), HIV seropositivity (1987), cutaneous and mucosal Kaposi's sarcoma (KS; 1992), perianal herpes simplex (1992), oral and esophageal candidiasis (1993), *Pneumocystis carinii* pneumonia (PCP; 1993), cytomegalovirus infection (1994), and *Mycobacterium avium intracellulare* (MAI) infection causing pulmonary disease (1995). His current medications included zidovudine (azidothymidine; AZT) used since 1989 and aerosolized pentamidine used monthly since 1991. Recent medical treatment for KS by means of systemic chemotherapy had been complicated by prolonged leukocytopenia and a low absolute neutrophil count.

Indirect laryngoscopy revealed a white lesion on the laryngeal surface of the epiglottis, the right aryepiglottic fold, the arytenoid, and the medial wall of

---

From the Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati, Cincinnati, Ohio (Tami), the Department of Otolaryngology–Head and Neck Surgery, University of Udine, Udine, Italy (Ferlito, Rinaldo), the Department of Otolaryngology, University of California San Francisco, San Francisco, California (Lee), and the Department of Otolaryngology, State University of New York Health Science Center at Brooklyn, Brooklyn, New York (Singh).

CORRESPONDENCE — Thomas A. Tami, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Cincinnati Medical Center, 231 Bethesda Ave, PO Box 670528, Cincinnati, OH 45267-0528.

the pyriform sinus. The laryngeal mobility was well preserved. No palpable cervical adenopathy was present. A preliminary diagnosis of laryngeal candidiasis was made, and the patient was treated with fluconazole (Diflucan) unsuccessfully. Two weeks later, he was evaluated by another otolaryngologist, who believed that the lesion was a laryngeal carcinoma. A biopsy performed under local anesthesia revealed inflamed and necrotic tissue with granules of actinomycetes and lymphocytes around small capillaries.

The patient was treated initially with oral doxycycline and subsequently with amoxicillin and clavulanate potassium with a good clinical response. Three weeks later, the patient's general condition began to deteriorate, and he was treated with intravenous piperacillin sodium. His medical condition continued to worsen and he died in May 1996, secondary to severe cachexia. A postmortem examination was not performed.

Comment. This case illustrates that actinomycosis can be difficult to diagnose and treat, in particular when unusual sites such as the larynx are involved. The initial clinical diagnosis of laryngeal candidiasis was changed to squamous cell carcinoma when antimycotic therapy was unsuccessful, but the definitive diagnosis of actinomycosis was only established after a biopsy specimen was obtained for histopathologic examination.

This patient was affected by a variety of unusual and opportunistic medical problems, including herpes zoster, cutaneous and mucosal KS, herpes simplex, oral and esophageal candidiasis, PCP, cytomegalovirus infection, MAI infection, and laryngeal actinomycosis — all conditions usually associated with an altered immune host system. Many opportunistic infections (viral, protozoal, fungal, and mycobacterial) and neoplasms (KS, nodal and extranodal non-Hodgkin's lymphoma, and possibly squamous cell carcinoma) can occur in AIDS patients and must be included in any differential diagnosis of an unusual or nonresponsive clinical presentation.

Despite its name, actinomycosis is a bacterial disease that is usually caused by the gram-positive anaerobe *Actinomyces israelii*, which is usually a harmless saprophyte of normal oral flora and is commonly found in the tonsillar crypts, gingiva, and other oral mucosa.[1] Immunosuppression is a common predisposing factor in patients who develop clinical infection with this organism, and its association with AIDS has been previously described.[2]

The 3 major forms of actinomycosis are classified according to anatomic site of involvement: cervicofacial (the most common manifestation), thoracic, and disseminated. Various focal presentation sites that have been reported in the head and neck include oral cavity, oropharynx, larynx, hypopharynx, nose, nasopharynx, paranasal sinuses, salivary glands, mandible, eye, and ear. Actinomycosis itself is a fairly uncommon infection; laryngeal actinomycosis is even more unusual, with fewer than 50 cases reported in the world literature.[1,3-9]

The clinical diagnosis of actinomycosis is often difficult to make and it can be easily confused with carcinoma, as demonstrated by this as well as other reported cases.[1] The microbiologic and histopathologic examinations are the most specific techniques for accurately making the diagnosis.[10] Microscopy will generally reveal gram-positive organisms, surrounding acute and chronic inflammation, foamy macrophages, and local tissue necrosis. The necrotic tissue usually contains colonies of microorganisms, the so-called "sulfur granules." The organism can usually be cultured from tissues and occasionally from blood.

The differential diagnosis should also include radionecrosis in patients previously treated with radiotherapy for laryngeal cancer, since several cases of laryngeal actinomycosis have occurred in this clinical setting.[3,9,11]

Penicillin is the drug of choice for the medical treatment of laryngeal actinomycosis. Prolonged treatment is often necessary; intravenous treatment is usually maintained for 4 to 6 weeks, followed by oral antibiotic therapy for at least 6 months. Patients who are allergic to penicillin can be given tetracycline.

CASE 2

A 41-year-old HIV-infected man presented to an otolaryngology clinic with a 3-month history of progressive hoarseness. This patient had a $CD4^+$ cell count of 50/mm^3. He had recently started on an intensive course of inhalational steroids for reactive airway disease, but was not receiving systemic steroids. Examination revealed white plaques on both mobile vocal cords. The remainder of the larynx was normal, and no other significant findings in the ears, nose, or throat were reported. The patient was empirically treated for several weeks with oral fluconazole for presumed laryngeal candidiasis.

After 1 month, the patient reported no symptomatic improvement. Indirect laryngoscopy suggested that the lesion had now extended onto the right false vocal cord; however, the vocal cords were still mobile. Direct laryngoscopy revealed a plaquelike lesion involving the right true and false vocal cords, the anterior commissure, and the anterior third of the left true vocal cord. A biopsy specimen was taken and cultures were obtained. *Aspergillus fumigatus* was isolated, and the patient was started on amphotericin B. Histologic examination revealed fungal organisms consistent with *Aspergillus* invading the laryngeal tissue. A computed tomography scan of the lungs, neck, and paranasal sinuses failed to reveal evidence of extralaryngeal fungal disease. The patient received several weeks of intravenous amphotericin B therapy in the hospital. Fiberoptic examination following 10 days of treatment revealed essentially no change. He was discharged on home intravenous amphotericin B therapy, but was readmitted 4 days later with fulminant PCP. Within 48 hours of admission, he died due to respiratory failure. An autopsy was refused by the patient's family.

Comment. Fungal infections of the larynx in the general population are extremely rare. In the medical literature, multiple case reports involving candidiasis, coccidioidomycosis, blastomycosis, histoplasmosis, and *Aspergillus* can be found.[12-16] Most of these cases were in immunocompetent patients with systemic or pulmonary fungal infections and concurrent laryngeal manifestations. Since HIV-infected patients are more susceptible to fungal and other opportunistic infections, reports involving these organisms have been increasing.[17] Most of these cases also included systemic infections.

The most common fungal organism to afflict the upper aerodigestive tract in HIV-infected patients is *Candida albicans*. Oral mucosal candidiasis is one of the earliest and most frequent manifestations of HIV infection, occurring even when a patient's $CD4^+$ cell count is over 500/mm^3.[18] As the $CD4^+$ cell count falls to less than 200/mm^3, patients become more susceptible to opportunistic infections, and these fungal infections often become more extensive and harder to treat. When patients with oral candidiasis complain of odynophagia and voice changes, mycotic infection of the larynx and/or esophagus should be suspected. Laryngeal lesions can be easily visualized with either indirect laryngoscopy or fiberoptic examination. Although the pseudomembranous type of lesion is the most commonly seen involving the larynx, atrophic or hypertrophic lesions can occur.[18] The pseudomembranous lesions are those white plaquelike lesions classically associated with oral candidal infections. Atrophic lesions are flat and hyperemic and are often mistaken for erythroplakia or telangiectasia. Hypertrophic lesions are thickened plaques, often with some white coloration. All of these candidal lesions rapidly respond to oral antifungal therapy. Although ketoconazole is effective for candidal infections, fluconazole in this patient group is better absorbed and better tolerated. Although, initially, empirical antifungal therapy for candidiasis is often given without biopsy, diagnostic direct laryngoscopy and biopsy is imperative if a substantial clinical response is not rapidly achieved. Cultures for fungal, as well as mycobacterial, organisms should be obtained in addition to histopathologic examination. Candidal infections in this patient population occasionally require more intensive medical therapy such as intravenous amphotericin B. There is no established therapeutic role for surgery. Relapses are frequent, and long-term prophylaxis for *Candida* is often necessary.

Another important mycotic infection in HIV-infected patients is aspergillosis. Although not common, invasive *A fumigatus* infections have been a well-recognized problem in immunocompromised patients.[19] In HIV-infected patients, increasing numbers of cases involving multiple sites have been reported. As in the case reviewed, most of these HIV-infected patients have $CD4^+$ cell counts of less than 50/mm^3. Most cases involve the lungs or the paranasal sinuses,[20,21] and although aspergillosis is not a common infection in the larynx, the overall increasing incidence of fungal infections in this patient population should lead to a more aggressive evaluation of laryngeal lesions. With more aggressive evaluation, earlier diagnosis will result in more effective treatment. The role of surgical debulking of this fungal infection prior to medical therapy with either itraconazole or amphotericin B remains unclear, and requires additional investigation.

As the incidence of AIDS continues to rise throughout the world, the occurrence of fungal infections endemic to certain geographic areas seems to be affecting this immunocompromised patient population (eg, histoplasmosis, coccidioidomycosis, and blastomycosis[22-24]). Since most of these cases occur in patients with a $CD4^+$ cell count of less than 100/mm^3, and they are usually associated with systemic fungemia and concurrent pulmonary symptoms, otolaryngologists who reside in these areas should be aggressive in performing diagnostic procedures to determine if these fungal organisms are responsible for laryngeal symptoms in this patient population.

CASE 3

A 42-year-old woman with a history of HIV infection and no prior AIDS-defining processes underwent a total laryngectomy and bilateral neck dissection followed by radiotherapy for a T4N2bM0 squamous cell carcinoma of the larynx. Pathologic examination of the surgical specimen revealed negative resection margins and absence of any lymphatic metastasis, including multiple 2-cm nodes in the posterior triangle of the neck. The patient's postoperative

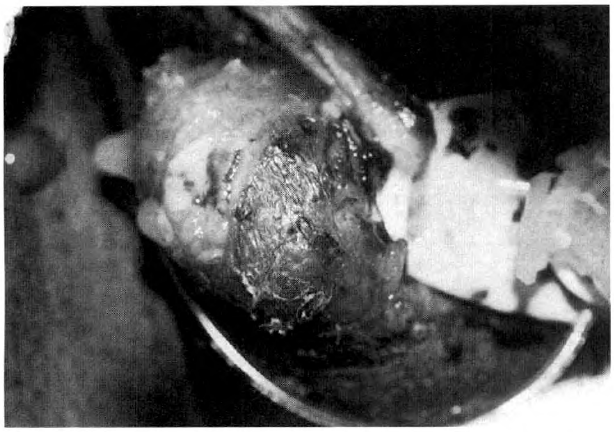


Fig 1. (Case 3) Recurrent aggressive squamous cell carcinoma at tracheal stoma, eroding through skin.

course was complicated by the development of a salivary fistula, which resolved with local care. In addition, her radiotherapy was interrupted for 2 weeks by the development of severe mucositis.

Soon after treatment completion, the patient developed a tracheostomal recurrence that rapidly extended to involve the nasopharynx (Fig 1). The patient succumbed to recurrent disease 3 months after treatment completion.

Comment. An increase in the incidence of laryngeal squamous cell carcinoma has been observed in patients with HIV infection; laryngeal involvement accounts for 63% of upper aerodigestive tract squamous cell carcinoma (UADT-SCC) in this patient population.[25,26] Although the pathogenetic factors involved in the development of laryngeal carcinoma in HIV-infected patients have yet to be determined, they likely center around dysfunctional immunity and tobacco and/or alcohol use, which are universal to affected patients[27] (also Singh et al, unpublished observations, 1996). This case demonstrates several alterations in presentation and course that accompany the increased incidence of laryngeal carcinoma in HIV-infected patients.

First, this patient's age reflects the younger age at which laryngeal cancer appears to develop in patients with HIV infection. Most patients with UADT-SCC and HIV infection present during the fourth decade of life, in contrast to HIV-negative patients, who present in the fifth and sixth decades[26] (also Singh et al, unpublished observations, 1996). In fact, concurrent HIV infection is present in up to 22% of patients less than 45 years of age with UADT-SCC.[26]

Second, as observed in this case, HIV-infected patients with UADT-SCC typically present with advanced (stage III or IV) disease[26] (also Singh et al, unpublished observations, 1996). However, tumor staging may be complicated in these patients by the multiple causes of cervical lymphadenopathy, resulting in clinical overstaging of neck nodal disease in up to 36% of cases.[26-29] (also Singh et al, unpublished observations, 1996). Overstaging of neck nodal involvement is caused by the suspicion of malignancy in enlarged posterior triangle lymph nodes, the most common head and neck site for progressive generalized lymphadenopathy in patients with HIV infection (86% of cases).[27,30,31] Since the posterior triangle is rarely involved by UADT-SCC, selective neck dissection may play a role in the management of selected cases; however, this approach probably needs further clarification.[32]

The presence of HIV infection seems to have a negative impact on the outcome of patients with laryngeal cancer. A trend toward an increased incidence of treatment-associated complications is seen in up to 50% of cases (Singh et al, unpublished observations, 1996). The most common of these are wound infection for surgical treatment, and mucositis for radiotherapy.[27] Careful preoperative planning and postoperative observation are required to limit both the incidence and severity of these complications. Also, tumor-specific survival is reduced, decreasing from 74% to 57% at 1 year and 59% to 32% at 2 years in the face of HIV infection.[26] The effect of HIV infection on survival remains significant even after controlling for the effects of stage and age.

These factors suggest that the development and progression of UADT-SCC may be accelerated in HIV-infected patients. Preliminary work has failed to show any gross histologic alterations in HIV-associated laryngeal carcinoma; however, one small study suggested an association between human papillomavirus infection and laryngeal carcinoma in patients with HIV infection, suggesting that viral infection may play an oncogenic or promoter role.[33] Although no studies have specifically evaluated the pathogenesis of HIV-associated laryngeal carcinoma, further research into HIV-associated UADT-SCC may open a window into the process of oncogenesis.

Alterations in current diagnostic and treatment philosophy are needed for the successful management of HIV-infected patients with laryngeal cancer. Traditional prognostic indicators in laryngeal carcinoma may not be of value in this patient population. Since the most consistent predictors of HIV-associated survival are $CD4^+$ cell count and the stage of HIV infection,[27] these factors must be taken into account in any accurate staging system and in treatment planning for these patients.

CASE 4

A 35-year-old HIV-infected homosexual man with

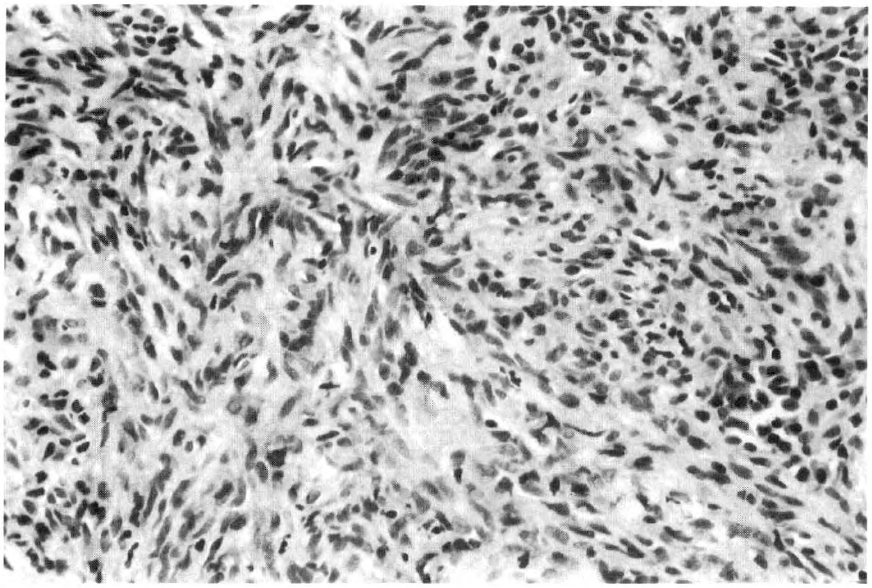


Fig 2. (Case 4) Histopathologic findings of Kaposi's sarcoma of larynx with typical spindle cell and vascular proliferation.

multiple cutaneous KS lesions presented with upper airway obstruction that had progressed over the previous week. He had no odynophagia; however, he did describe dysphagia due to persistent aspiration. On physical examination, he had multiple cutaneous facial KS lesions and generalized cervical lymphadenopathy. He had obvious stridor and air hunger. Fiberoptic laryngoscopy revealed a large violaceous mass on the right side of the epiglottis and right aryepiglottic fold. The endolarynx and glottis were obscured by this supraglottic mass.

The patient was taken immediately to the operating room, where a tracheotomy was performed. Direct laryngoscopy revealed a lesion as previously described that was confined to the supraglottic larynx. In the setting of multiple associated cutaneous KS lesions, a working diagnosis of laryngeal KS was made and subsequently confirmed with a biopsy (Fig 2). The patient was offered subsequent therapy with low-dose external-beam irradiation. He was treated successfully, and was decannulated approximately 1 month following completion of therapy.

Comment. Prior to the early 1980s, KS was never on the differential diagnosis of patients presenting with laryngeal problems. In fact, this unusual tumor was classically described only in elderly Jewish or Mediterranean men and occurred primarily on the lower extremities. However, following the initial descriptions of patients with AIDS, beginning in the early 1980s, KS has become an integral part of the pathologic process in these patients and is the most common malignancy associated with AIDS.[34]

Interestingly, KS is encountered predominantly in homosexual men who develop AIDS, and is only rarely described in other HIV-infected populations. This peculiar association has stimulated substantial investigation into the possibility of an infectious agent other than HIV that may be responsible for these tumors. A herpeslike virus has recently been implicated as the causative agent for KS in the homosexual HIV-infected population.[35]

Kaposi's sarcoma of the upper aerodigestive tract is not unusual; the palate and gingiva are the most frequently involved sites.[36] The larynx is usually involved only with advanced HIV infection. As with any laryngeal disorder, the presenting symptoms can range from hoarseness and dysphagia to stridor or complete airway obstruction. Fortunately, in the presence of other widespread manifestations of KS, the diagnosis can usually be easily established by fiberoptic laryngeal examination. Histopathologic evaluation of biopsy specimens will reveal spindle-shaped cells with a random orientation, many extravasated erythrocytes, and thin vascular slits occurring in a reticular network of collagen fibers.

After establishing the diagnosis, therapy is usually directed at palliating symptoms. Urgent intervention must be considered for lesions producing acute or impending airway obstruction. Tracheotomy should be immediately offered to these patients so that further diagnostic and therapeutic options can be pursued. Treatment for KS includes an array of systemic and local therapies. Systemic therapy is usually reserved for patients with rapidly progressing and/or widespread disease. Adriamycin, bleomycin sulfate, and vincristine sulfate have been associated with a response rate as high as 88%.[37] Immune response modifiers such as interferon-α have also been somewhat effective for long-term therapy of KS.[38]

Local therapy is usually used to palliate pain and to improve function. Radiotherapy is often effective at doses ranging from 2,000 to 3,000 cGy; however, severe mucositis can result if higher doses are used on mucosal areas. Intralesional chemotherapy using vinblastine sulfate has also been established as an effective alternative for localized cutaneous and oral mucosal lesions. Successful application of this technique has also been reported for lesions of the supraglottic larynx.[39] Local ablation with the carbon dioxide laser may also be effective for localized KS lesions.

Laryngeal KS always presents a challenge, since the risk of airway obstruction is ever present. Tracheotomy should always be considered prior to any treatment protocol, since local therapy can often exacerbate airway compromise as mucositis and soft tissue edema develop.[40]

DISCUSSION

As illustrated by these 4 cases, the list of potential diseases that can be encountered in the larynx in patients infected with HIV is staggering. Currently, the World Health Organization estimates that there are over 20 million HIV-infected people worldwide, and that this number may double by the turn of the century. This tremendous growth in the HIV-infected population will undoubtedly have an impact on otolaryngologists, who will be increasingly faced with diagnostic and treatment dilemmas such as those described above. To deal effectively with the varied manifestations of this disease, otolaryngologists will be forced to become reacquainted with the wide array of infectious and neoplastic conditions that can occur in the larynx.

When laryngeal lesions or conditions do not immediately respond to standard conservative measures, the differential diagnosis must be immediately extended to include unusual infections or neoplastic problems. If the patient is not known to be HIV-infected, HIV and other causes of immune dysfunction should probably be pursued and investigated. If an infectious disease is suspected, empiric use of antifungals can be considered; however, early biopsy and culture should be obtained to establish the diagnosis and to direct appropriate antimicrobial therapy. In instances of both infectious and neoplastic processes, airway compromise may be immediate or impending, and tracheotomy should be part of the early management. Since some of these conditions can progress rapidly, an accurate diagnosis should be arrived at as early as possible so that the institution of a treatment plan is not delayed.

Recent therapeutic advances in the management of HIV disease have created a tremendous stir in the medical and infectious disease community. The recent apparent clinical success of the protease inhibitor class of anti-AIDS drugs when used in combination with older anti-retroviral agents has created an air of optimism among both AIDS specialists and patients.[41] If early clinical enthusiasm results in long-term remissions for HIV-infected patients, we may be on the verge of converting what was once a universally fatal disease into a chronic medical condition that can be controlled with appropriate medications. In light of these exciting prospects, the approach to even advanced infectious and neoplastic diseases in HIV-infected patients must now be undertaken in a more aggressive manner. Palliation is certainly important, but clinical cure must now be used as the goal of therapy in even severely immunocompromised patients, since they may ultimately show dramatic responses to these new treatment regimens.

In summary, unusual infectious and neoplastic diseases can occur in the larynx in patients with advanced HIV disease. The keys to successful management of these patients include the following.

1. A high index of suspicion when laryngeal problems fail to respond to otherwise standard empiric medical therapy.
2. A differential diagnosis that includes even unusual infectious and neoplastic conditions.
3. An understanding that these conditions can act much more aggressively and spread more rapidly in this severely immunocompromised patient population.
4. Consideration of airway compromise and tracheotomy offered as a viable therapeutic option.
5. Aggressive diagnosis and therapeutic intervention in all patients, including those with severe AIDS-related immunodeficiency, as a new era of AIDS therapy may have emerged with the recent introduction of protease inhibitors.

REFERENCES

1. Hughes RA Jr, Paonessa DF, Conway WF Jr. Actinomycosis of the larynx. Ann Otol Rhinol Laryngol 1984;93:520-4.

2. Kingdom T, Tami T. Actinomycosis of the nasal septum in a patient infected with the human immunodeficiency virus. Otolaryngol Head Neck Surg 1994;111:130-3.

3. Nelson EG, Tybor AG. Actinomycosis of the larynx. Ear Nose Throat J 1992;71:356-8.

4. Beysiegle K. Aktinomykose des Ohres und Kehlkopfs. Int Z Ohrenheilkd 1933;36:157-72.

5. Hoffman R. Uber Aktinomykose des Kehlkopfes und des Kopfnickers. MMW 1909;53:449-53.

6. Daffas J. Mycoses et cancer du larynx. Rev Laryngol Otol Rhinol (Bord) 1939;60:523-46.

7. Vergues F. Un cas d'actinomycose pharyngo-laryngee.

Rev Laryngol Otol Rhinol (Bord) 1942;63:141-3.

8. Shaheen S, Ellis FG. Actinomycosis of the larynx. J R Soc Med 1983;76:226-9.

9. Tsuji D, Fukuda H, Kawasaki Y, Kawaida M, Ohira T. Actinomycosis of the larynx. Auris Nasus Larynx 1991;18:79-85.

10. Emmanuelli J. Infectious granulomatous diseases of the head and neck. Am J Otolaryngol 1993;14:155-67.

11. Langnickel R. Primare Aktinomykose des Larynx. Z Laryngol Rhinol Otol 1972;51:147-52.

12. Fletcher S, Prussin A. Histoplasmosis of the larynx treated with ketoconazole: a case report. Otolaryngol Head Neck Surg 1990;103:813-6.

13. Ferlito A. Primary aspergillosis of the larynx..J Laryngol Otol 1974;88:1257-63.

14. Selkin S. Laryngeal candidiasis and ketoconazole. Otolaryngol Head Neck Surg 1985;93:661-3.

15. Boyle J, Coulthard S, Mandel R. Laryngeal involvement in disseminated coccidioidomycosis. Arch Otolaryngol Head Neck Surg 1991;117:433-8.

16. Bradsher R. Histoplasmosis and blastomycosis. Clin Infect Dis 1996;22:S102-S111.

17. Vrabec D. Fungal infections of the larynx. Otolaryngol Clin North Am 1993;26:1091-114.

18. Dichtel W. Oral manifestations of human immunodeficiency virus infection. Otolaryngol Clin North Am 1992;25: 1211-26.

19. Lorthollary O, Meyohas M, Dupont B, Cadranel J, Salmon-Ceron D, Simonin D. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. Am J Med 1993;95:177-87.

20. Kingdom T, Lee K. Invasive aspergillosis of the larynx in AIDS. Otolaryngol Head Neck Surg 1996;115:135-7.

21. Richardson B, Morrison V, Gapany M. Invasive aspergillosis of the larynx: case report and review of the literature. Otolaryngol Head Neck Surg 1996;114:471-3.

22. Sarosi G. Endemic mycosis complicating human immunodeficiency virus infection. West J Med 1996;164:335-40.

23. Wheat J. Mycosis in AIDS: a clinical review. Clin Microbiol Rev 1995;8:146-59.

24. Hajjeh R. Disseminated histoplasmosis in patients infected with human immunodeficiency virus. Clin Infect Dis 1995;21(suppl 1):S108-S110.

25. Gachupin-Garcia A, Selwyn P, Budner N. Population-based study of malignancies and HIV infection among injecting drug users in New York City methadone treatment program, 1985-1991. AIDS 1991;6:843-8.

26. Singh B, Sabin S, Har-El G, Lucente F. Upper aerodigestive tract squamous cell carcinoma: the human immunodeficiency virus connection. Arch Otolaryngol Head Neck Surg 1996;122:639-43.

27. Lucente F, Singh B, Har-El G. Cancer of the head and neck in HIV infected patients. In: Myers EN, Suen J, eds. Cancer of the head and neck. 3rd ed. Philadelphia, Pa: WB Saunders, 1996:625-43.

28. Singh B, Balwally A, Nash M, Har-El G, Lucente F. Laryngeal tuberculosis: a difficult diagnosis. Laryngoscope 1996; 106:1238-40.

29. Finn D. Lymphoma of the head and neck and acquired immunodeficiency syndrome: clinical investigation and immunohistochemical study. Laryngoscope 1995;105:1-18.

30. Abrams D, Lewis B, Beckstead J. Persistent diffuse lymphadenopathy in homosexual men: end point or prodrome? Ann Intern Med 1984;100:801-5.

31. Abrams D. AIDS-related lymphadenopathy: the role of biopsy. J Clin Oncol 1986;4:126-7.

32. Davidson B, Kulkarny V, Delacure M. Posterior triangle metastases of squamous cell carcinoma of the upper aerodigestive tract. Am J Surg 1993;166:395-8.

33. Roland J, Roghstein S, Mittal K. Squamous cell carcinoma in HIV positive patients under 45. Laryngoscope 1993; 103:509-11.

34. Northfelt D, Kahn J, Volberding P. Treatment of AIDS-related Kaposi's sarcoma. Hematol Oncol Clin North Am 1991; 5:297-310.

35. Orenstein JM, Alkan S, Blauvelt A, et al. Visualization of human herpesvirus type 8 in Kaposi's sarcoma by light and transmission electron microscopy. AIDS 1997;11:F35-F45.

36. Lozada F, Silverman S Jr, Migliorati CA, Conant MA, Volberding PA. Oral manifestations of tumor and opportunistic infections in the acquired immunodeficiency syndrome (AIDS): findings in 53 homosexual men with Kaposi's sarcoma. Oral Surg Oral Med Oral Pathol 1983;56:491-4.

37. Gill PS, Rarick M, McCutchan JA, et al. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. Am J Med 1991;90:427-33.

38. Rios A, Mansell P, Newell G. Treatment of acquired immunodeficiency syndrome–related Kaposi's sarcoma with lymphoblastoid interferon. J Clin Oncol 1985;3:506-12.

39. Tami T, Sharma P. Intralesional vinblastine therapy for Kaposi's sarcoma of the epiglottis. Otolaryngol Head Neck Surg 1995;113:283-5.

40. Tami T, Sharma P. Laryngeal manifestations of AIDS. In: Fried M, ed. The larynx. St Louis, Mo: Mosby–Year Book, 1996.

41. Collier A, Coombs RW, Schoenfeld D. Treatment of human immunodeficiency virus infection with siquinavir, zidovudine, and zalcitabine. N Engl J Med 1996;334:1011-7.

Ann Otol Rhinol Laryngol 108:1999

VIRTUAL LARYNGOSCOPY

MARVIN P. FRIED, MD
BOSTON, MASSACHUSETTS

VIK M. MOHARIR, MD
BOSTON, MASSACHUSETTS

HIROSHI SHINMOTO, MD
TOKYO, JAPAN

ABDALMAJEID M. ALYASSIN, PHD
SCHENECTADY, NEW YORK

WILLIAM E. LORENSEN, MS
SCHENECTADY, NEW YORK

LIANGGE HSU, MD
BOSTON, MASSACHUSETTS

RON KIKINIS, MD
BOSTON, MASSACHUSETTS

Virtual endoscopy enables computer-generated 3-dimensional visualization of a cavity by reconstructing 2-dimensional computed tomographic or magnetic resonance data. The technique has been used experimentally to study the colon, bronchi, ears, and other structures. Here, virtual laryngoscopies were created from the cross-sectional image data of 3 patients. The cases represented a normal airway, a squamous cell carcinoma of the glottic fold, and a posterior glottic stenosis. These reconstructions included extraluminal anatomy that is not typical of current virtual endoscopic techniques. The 2-dimensional computed tomographic and magnetic resonance images of the patients underwent post-processing for 3-dimensional reconstruction. The resulting models were imported into an experimental virtual endoscopy program for 1) airway lumen generation and 2) interactive viewing. Though they could not be used for biopsy, the virtual laryngoscopies provided, in a noninvasive fashion, good simulation of endoscopy. Virtual endoscopy also gave the added benefits of the ability to assess the transmural extent of disease and view the airway distal to areas of luminal compromise. This technology may well provide clinical benefit in preoperative planning, staging, and intraprocedural guidance for head and neck disease and merits further study.

KEY WORDS — computer-assisted imaging, head and neck, larynx, three-dimensional reconstruction, virtual endoscopy.

INTRODUCTION

Endoscopy is used diagnostically for detailed 3-dimensional (3-D) evaluation of a lumen or cavity. Some disadvantages of endoscopic examinations, including those of the larynx, are that they require sedation, one cannot assess beyond areas that prevent passage of the endoscope, and viewing is limited strictly to the lumen, restricting transmural evaluation of lesions. There is also a risk of viscus perforation in procedures such as esophagoscopy. Virtual endoscopy provides 3-D anatomic information by reconstructing 2-dimensional (2-D) computed tomography (CT) and magnetic resonance imaging (MRI) data, overcoming the drawbacks of endoscopy. The colon, bronchi, ears, and other structures[1-6] have served for initial assessment of virtual endoscopy. The advantage of 3-D visualization of the larynx makes this a desirable area for virtual endoscopy, despite the fact that it cannot be used for biopsy. The benefits of virtual laryngoscopy should be particularly helpful during assessment of the difficult airway or when neoplasia, infection, inflammation, or congenital defects compromise the lumen.

Current methods of virtual endoscopy are limited in their 3-D display of extraluminal anatomy. For example, during virtual bronchoscopy, blood vessels and the lung parenchyma are often not seen. The lack of a global context and physical clues during viewing may lead to confusion of the patient's anatomy.[7] We address this problem by incorporating into our virtual endoscopic technique a method of 3-D anatomic reconstruction that can use merged CT and magnetic resonance images. In this paper, we describe our virtual endoscopic technique, augmented by 3-D anatomic reconstruction, and discuss our initial results with virtual laryngoscopy.

MATERIALS AND METHODS

Patient Profile. In order to give a variety of clinical conditions, 3 cases were chosen retrospectively

---

From the Department of Otology and Laryngology, Harvard Medical School, and the Joint Center for Otolaryngology, Beth Israel–Deaconess Medical Center and Brigham and Women's Hospital (Fried, Moharir), the Surgical Planning Laboratory, Division of MRI and Image Guided Therapy Program, Department of Radiology, Harvard Medical School and Brigham and Women's Hospital (Shinmoto, Kikinis), and the Division of Neuroradiology, Department of Radiology, Harvard Medical School and Brigham and Women's Hospital (Hsu), Boston, Massachusetts, and the General Electric Corporate Research and Development Center, Schenectady, New York (Alyassin, Lorensen). This work was supported in part by grants from The Partner's Center for Innovative Minimally Invasive Therapy; Sun Microsystems; General Electric; International Business Machines; Pharmacia and Upjohn; Carl Zeiss, Inc; Thinking Machines, Inc; The National Institutes of Health (grants R01 CA46627-08, P01 CA67165-01A1, and P01 AG04953-14); The Whitaker Foundation; The Whittaker Corporation; the Department of Radiology, Brigham and Women's Hospital; and Harvard Medical School.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, May 9-10, 1998.

CORRESPONDENCE — Marvin P. Fried, MD, 333 Longwood Ave, Boston, MA 02115.

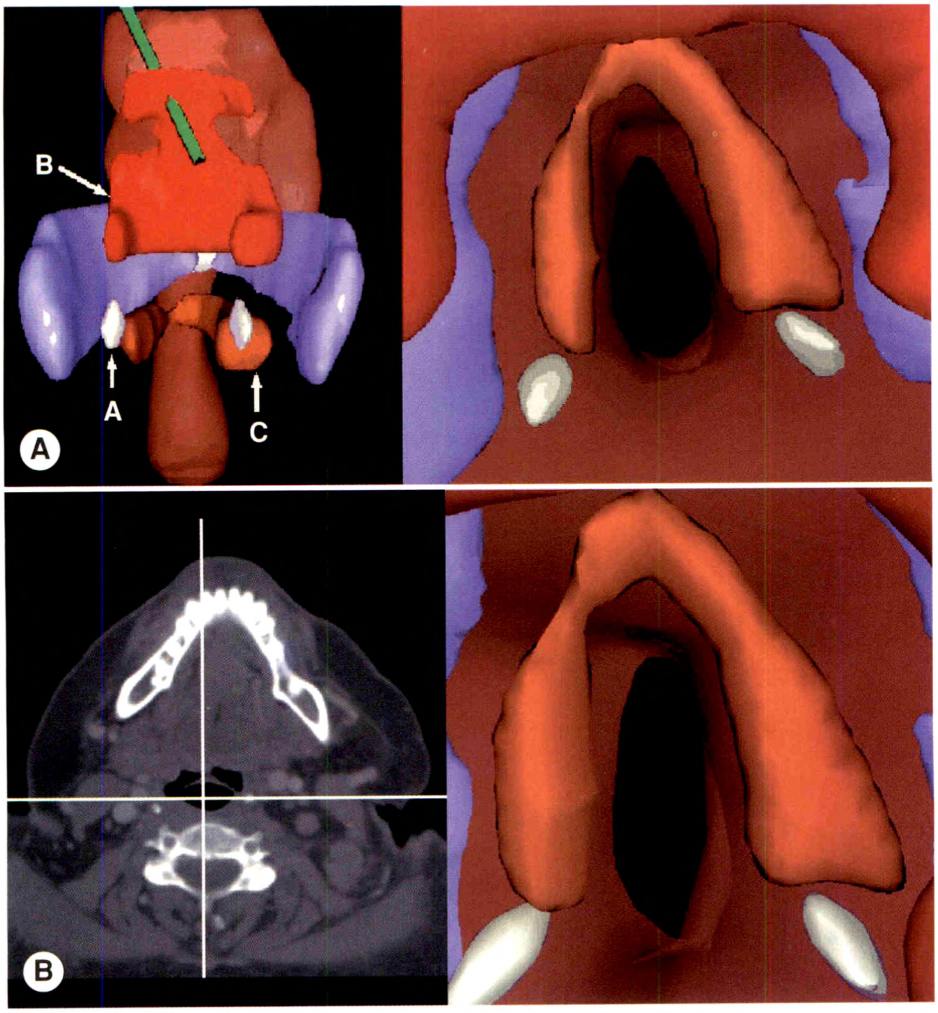


Fig 1. (Patient 1) A) Left side shows posterior global view of virtual endoscopy. Left ("A") and right arytenoid cartilages are in white. Lumen has been rendered partially transparent to show thyroid cartilage (in violet). Epiglottis is in red, along with aryepiglottic fold and cuneiform tubercle ("B"). Vocal folds ("C") are rendered orange. Green line follows along to indicate camera position during virtual endoscopy. Camera faces inferiorly to give us view on right, showing vocal folds, arytenoid cartilages, edge of cuneiform tubercle, and thyroid cartilage. B) Right side shows view of larynx further along during virtual endoscopy. Vocal folds are in orange, arytenoid cartilages are in white, and epiglottis, located along superior and right perimeter, is in red. Lumen has been rendered partially transparent to expose thyroid cartilage, in violet. On left, instead of global view, we see related 2-dimensional computed tomography slice. Crosshairs indicate camera location, which faces inferiorly to show camera view on right. Related computed tomography slices scroll along during virtual endoscopy to continuously update camera location.

for virtual laryngoscopy. Patient 1 (Fig 1) is a 56-year-old woman with no laryngeal or airway disease. Patient 2 (Fig 2) is a 58-year-old man with a T3N3M0 squamous cell carcinoma involving the area of the left vocal fold, with paraglottic extension. Patient 3 (Fig 3) is a 39-year-old woman with posterior laryngeal glottic stenosis.

Data Acquisition. Patient 1 underwent a helical CT scan with 3-mm-thick axial images. Patient 2 underwent CT and MRI. The CT consisted of 5-mm-thick consecutive axial images, while MRI was acquired with 1.5-cm-thick axial spoiled grass (SPGR) images. Patient 3 underwent a helical CT scan with 2-mm-thick axial images.

Image Processing. All 3 patients underwent 3-D reconstruction of their anatomy. Patient 1 had the following structures reconstructed: vocal folds, thyroid cartilage, arytenoid cartilage, epiglottis, and cuneiform tubercle. For patient 2, the following structures were assembled: epiglottis, tumor, left jugular vein, left common carotid artery, vertebral column, hyoid bone, and mandible. Last, patient 3 had the following anatomic entities reconstructed: hyoid bone, thyroid cartilage, vocal folds, epiglottis, arytenoid cartilages, and intra-arytenoid web.

The 3-D reconstruction method employed was developed at The Surgical Planning Laboratory of Brigham and Women's Hospital. The CT and MRI images were transferred to computer workstations at the laboratory by means of internal network communication. The images underwent filtering for reduction of unwanted signal.[8] Registration, or merging, of CT and MRI images came next for patient 2. The matrix of the CT images was reduced from 512 to 256 in order to match the MRI data. The actual combining then took place, based on maximization of mutual information between aligned CT and MRI images.[9] The rest of the steps utilized these combined data, allowing information from the two different radiologic modalities to be incorporated into the final picture. Segmentation consisted of isolating and outlining each desired anatomic component in the 2-D radiologic data.[10] This involved an automatic component and a manual component and was the rate-limiting step of the entire reconstruction process. After an individual anatomic component was

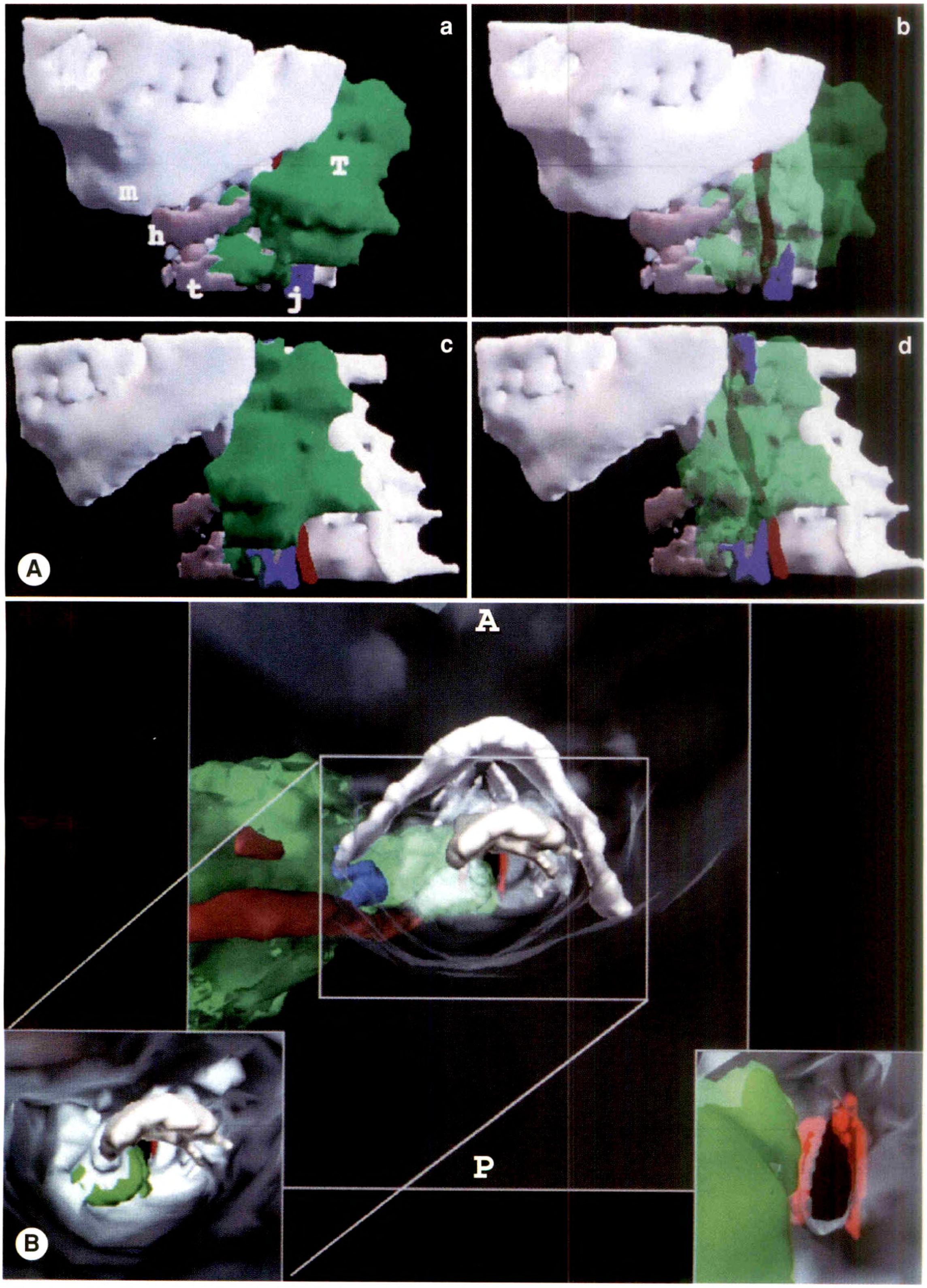
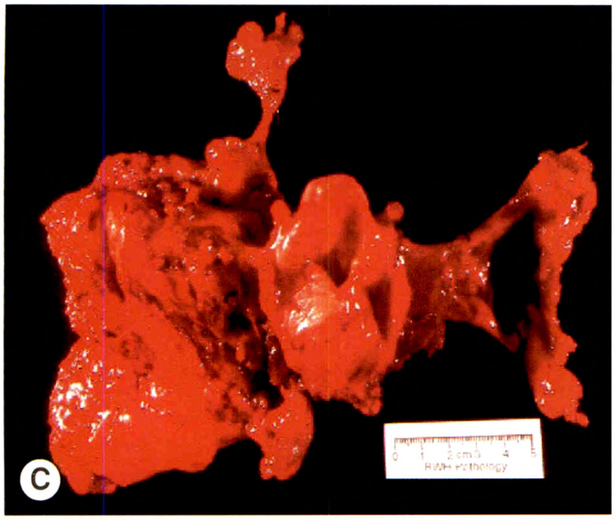


Fig 2. (Patient 2) A) Multiple global views. a and b are frontal-lateral views, with tumor (T) transparent in b. Carotid artery, in red, is patent; jugular vein (j), in blue, is compressed. c and d are left lateral views, with tumor transparent in d. m — mandible, h — hyoid bone, t — thyroid cartilage. B) Different images of virtual endoscopy. Left image displays airway with walls opaque. Epiglottis is in off-white and tumor in green. Center figure shows walls transparent. Transmural extent of tumor and its relationship to surrounding structures are seen. Right image displays virtual camera view further down airway, with walls made partially transparent. Vocal cords (red) and tumor are visualized. A — anterior, P — posterior. (Continued on next page.)



(Fig 2, continued.) C) Gross pathology, posterior view. Larynx and contents of dissected right and left sides of neck are shown. As confirmed intraoperatively, virtual laryngoscopy well demonstrated findings of extent of disease, penetration outside of larynx, and occlusion of left jugular vein.

segmented, the slices were stacked together to form a 3-D anatomic structure.[11-13] In a viewing program, the individual structures were integrated to create a 3-D model of the patient anatomy.

The completed 3-D models were imported into an experimental virtual endoscopy program[14] (VESA, General Electric Corporate Research and Development Center, Schenectady, NY). Inclusion of the models in the virtual endoscopy program was feasible because both use the visualization tool kit format for displaying 3-D images.[15] The virtual endoscopy program then created the airway lumen of each patient, starting at the oropharynx and ending at the trachea. Last, a virtual laryngoscopy path was generated, also by the program, by marking start and end points on the axial CT images.

RESULTS

The virtual laryngoscopies were run on a computer workstation (Ultrasparc with Creator 3-D graphics, Sun Microsystems, Mountain View, Calif). The virtual endoscopy program allowed for display of multiple images, a camera view, a global or external view, and a view of the related CT or MRI slice. The camera and global views could be enlarged or reduced, rotated 360° in any axis, and translocated in the vertical or horizontal plane. The camera lens could face any direction and have a view angle from 1° to 180°. Any anatomic structure could be added or deleted. The individual anatomic components could be rendered transparent and have their color and light intensity controlled.

The virtual endoscopy of patient 1 (Fig 1) started in the oropharynx. The camera faced inferiorly as it descended the airway. It moved past the arytenoid cartilage and vocal folds and into the trachea. Rendering the airway lumen transparent shows the thyroid cartilage. While in the trachea, turning the camera

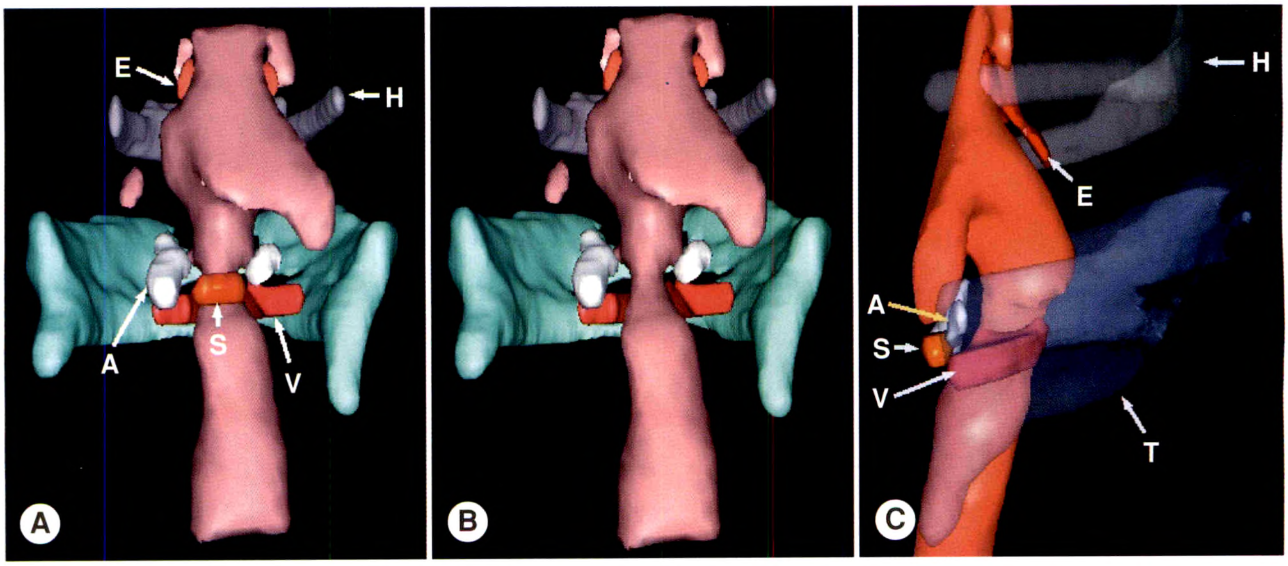


Fig 3. (Patient 3) A) Posterior global view of virtual laryngoscopy. Airway lumen is in peach and thyroid cartilage is rendered light green. A — left arytenoid cartilage, S — stenotic intra-arytenoid web, V — right vocal fold, H — hyoid bone, E — epiglottis. B) Another posterior global view during virtual laryngoscopy. Key difference between this Figure and A is that intra-arytenoid web is rendered invisible here. Airway lumen narrowing between arytenoid cartilages (white) and vocal folds (orange) is evident. Below vocal folds, diameter of airway lumen expands, giving no further evidence of stenosis. C) Lateral global view of virtual endoscopy. Airway lumen, in orange, runs superior to inferior. Hyoid bone (H) and thyroid cartilage (T) have been rendered transparent. E — epiglottis, A — right arytenoid cartilage, S — stenotic intra-arytenoid web, V — vocal fold.

in the cephalic direction gave an inferior view of the laryngeal structures. The virtual endoscopy screen gave the camera location in a global context, as well as the related cross-sectional CT slice.

The virtual laryngoscopy of patient 2 (Fig 2) began in the oropharynx. The camera looked down toward the epiglottis, beyond which the tumor protruded into the larynx. The transparent airway lumen and the global view allowed for appreciation of the transmural extent of the tumor. In addition, a patent left common carotid artery and compressed jugular vein could be seen. The resected gross pathology specimen confirmed the virtual laryngoscopy findings of extension outside the limits of the larynx and of occlusion of the jugular vein.

The virtual endoscopy of patient 3 (Fig 3) began in the oropharynx. It looked down toward the vocal folds. The area of stenosis was visualized on both the camera and global views. During endoscopy, we could not view beyond the glottis; however, the virtual camera moved beyond the vocal folds and the area of stenosis without difficulty. A retroverted view from the trachea gave another perspective on the laryngeal structures. A posterior global view, with the web removed, demonstrated a noncompromised airway distal to the stenosis.

DISCUSSION

Physicians use a variety of imaging techniques for diagnosis, staging, preoperative planning, and monitoring of disease. Endoscopy allows for direct viewing into a cavity. In addition to being an invasive procedure and requiring sedation, endoscopy cannot be used beyond areas of luminal stenosis or obstruction and limits visualization to the interior walls of the cavity. Both CT and MRI show tissue volume beyond the lumen and usually do not require sedation. The problem with these noninvasive techniques is that they present information in a cross-sectional 2-D format, which the physician must mentally reconstruct into a 3-D picture. This at times can be difficult in areas of intricate anatomy, such as that of the head and neck.[16] Having 3-D imaging from noninvasive techniques could combine the benefits of endoscopic and radiologic imaging.

Previous researchers used CT for 3-D reconstruction of the larynx and airway.[17-20] Because CT has poor soft tissue resolution, using it alone would make evaluation of head and neck tumors difficult. Dunham and Wolf[21] digitized endoscopic images of the pediatric airway and used a computer for 3-D reconstruction of the lumen. Though it allows the airway to be visualized in 3 dimensions, this method cannot be used to display extraluminal anatomy or the transmural extent of tumors.[21]

Virtual endoscopy uses 2-D CT and MRI data to create a 3-D emulation of endoscopy with some important advantages. By making the lumen transparent during virtual endoscopy, the full extent of a lesion may be seen, as demonstrated by the case study of patient 2. This may enhance preoperative planning and staging of head and neck disorders. Endoscopy is limited by the physical progression of an endoscope; this presents a problem when assessing a difficult airway, such as a lumen narrowed from any cause. An example occurred during the evaluation of patient 3; during the endoscopic examination, we could not view beyond the stenosis. Virtual endoscopy allowed for visualization beyond the lesion without difficulty.

A technical challenge to current methods of virtual endoscopy is the limitation of anatomic detail. Our approach to virtual endoscopy incorporates a method of 3-D anatomic reconstruction to better delineate patient anatomy. This new technique allows for anatomic rendition of even the smallest of structures, such as the vocal folds and arytenoid cartilages. Combined MRI and CT data allow for visualization of soft tissue, cartilage, and bone. This should be particularly helpful when evaluating tumors and their extension. As demonstrated by the second case study, the intricate relationship of the tumor with its surrounding viscera, such as the occluded jugular vein and patent carotid artery, could be delineated. The simultaneous display of the global view and related CT or MRI slices further improved the understanding of the location of the virtual camera in relation to its extraluminal spatial context.

It is important to stress that virtual endoscopy, unlike traditional endoscopy, cannot be used for biopsy. However, combining the two techniques by integrating and displaying virtual endoscopy during endoscopic procedures may have a synergistic effect. This could allow for biopsy of the margins of lesions, improving delineation of the extent of disease.[16,22] The neurosurgical team of our institution is already using this technology for intraprocedural guidance,[23] and in the near future, we hope to do so as well.

We did encounter some challenges that must be overcome before expanded application of our method of virtual laryngoscopy. The 3-D anatomic rendition is only as good as the 2-D CT and MRI images from which it is constructed. The luminal views are inferior in detail to their endoscopic counterparts. Currently, it takes several hours for completion of a single virtual endoscopy, not including the steep learning curve that exists. If 3-D anatomic reconstruction is not incorporated, virtual endoscopy of the lumen and limited structures takes approximately 1 to 2 hours, with less of a learning curve for the individual doing the reconstruction. The current cost for incorporating 3-D reconstruction into virtual endoscopy needs reduction. Finally, the key question remains: What role should virtual laryngoscopy, with or without 3-D reconstruction, play in the clinical setting? This can only be answered with further study and clinical correlation.

CONCLUSION

A new approach to virtual endoscopy now exists by adding 3-D anatomic reconstruction. It provided good representation of the laryngeal and neck anatomy of the 3 patients that served as the initial study group. Though it cannot be used for biopsy, virtual laryngoscopy carries potential for improving preoperative planning, staging, and intraprocedural guidance for head and neck pathology. However, prior to expanded implementation, improvements need to be made in time and cost factors. In addition, a study with a larger patient population needs to be done in order to compare virtual laryngoscopy with intraoperative findings.

ACKNOWLEDGMENT — The authors thank Dr Ferenc Jolesz, Chief, Brigham and Women's Hospital Division of MRI, for his significant and valuable support of this project.

REFERENCES

1. Vining DJ, Shifrin RY, Grishaw EK. Virtual colonoscopy [Abstract]. Radiology 1994;193:446.

2. Vining DJ, Liu K, Choplin RH, Haponik EF. Virtual bronchoscopy: relationships of virtual reality endobronchial simulations to actual bronchoscopic findings. Chest 1996;109:549-53.

3. Frankenthaler R, Moharir VM, Kikinis R, et al. Virtual otoscopy. Otolaryngol Clin North Am 1998;31:383-92.

4. Satava RM, Simon IB. Endoscopy for the year 2000. Gastrointest Endosc Clin N Am 1993;4:397-407.

5. Jolesz FA, Lorensen WE, Shinmoto H, et al. Interactive virtual endoscopy. AJR Am J Roentgenol 1997;169:1229-35.

6. Geiger B, Kikinis R. Simulation of endoscopy. In: Ayache N, ed. Lecture notes in computer science. Proceedings of The First International Conference on Computer Vision, Virtual Reality, and Robotics in Medicine, Nice, France, 1995;905:277-81.

7. Summers RM. Navigational aids for real-time virtual bronchoscopy. AJR Am J Roentgenol 1997;168:1165-70.

8. Gerig G, Kubler O, Kikinis R, Jolesz FA. Nonlinear anisotropic filtering of MRI data. IEEE Trans Med Imaging 1992;11:221-32.

9. Wells W, Viola P, Kikinis R. Multi-modal volume registration by maximization of mutual information. Med Image Analysis 1996;1:35-51.

10. Wells WM, Grimson WE, Kikinis R, Jolesz FA. Adaptive segmentation of MRI data. IEEE Trans Med Imaging 1996; 15:429-42.

11. Lorensen W, Cline H. Marching cubes: a high resolution 3D surface construction algorithm. Comput Graph 1987;21:163-89.

12. Schroeder W, Zarge J, Lorensen W. Decimation of triangle meshes. Comput Graph 1992;26:65-70.

13. Taubin G. Curve and surface smoothing without shrinkage. IBM Research Report RC-19536, 1994.

14. Alyassin AM, Lorensen WE. Virtual endoscopy software applications on a PC. Proceedings of the Sixth Annual Conference on Medicine Meets Virtual Reality, San Diego, Calif, 1998: 84-9.

15. Schroeder W, Martin K, Lorensen W. The visualization toolkit. 2nd ed. Englewood Cliffs, NJ: Prentice-Hall, 1997.

16. Jolesz FA. Image-guided procedures and the operating room of the future. Radiology 1997;204:601-12.

17. Silverman PM, Zeiberg AS, Sessions RB, Troost TR, Zeman RK. Three-dimensional imaging of the hypopharynx and larynx by means of helical (spiral) computed tomography. Comparison of radiological and otolaryngological evaluation. Ann Otol Rhinol Laryngol 1995;104:425-31.

18. Zinreich SJ, Mattox DE, Kennedy DW, et al. 3-D CT for cranial facial and laryngeal surgery. Laryngoscope 1988;98: 1212-9.

19. Metes A, Hoffstein V, Direnfeld V, Chapnick JS, Zamel N. Three-dimensional CT reconstruction and volume measurements of the pharyngeal airway before and after maxillofacial surgery in obstructive sleep apnea. J Otolaryngol 1993;22:261-4.

20. Yumoto E, Sanuki T, Hyodo M, Yasuhara Y, Ochi T. Three-dimensional endoscopic mode for observation of laryngeal structures by helical computed tomography. Laryngoscope 1997;107:1530-7.

21. Dunham ME, Wolf RN. Visualizing the pediatric airway: three-dimensional modeling of endoscopic images. Ann Otol Rhinol Laryngol 1996;105:12-7.

22. Fried MP, Hsu L, Topulos G, Jolesz FA. Image-guided surgery in a new magnetic resonance suite: preclinical considerations. Laryngoscope 1996;106:411-7.

23. Nakajima S, Atsumi H, Kikinis R, et al. Use of cortical surface vessel registration for image-guided neurosurgery. Neurosurgery 1997;40:1201-8.

Ann Otol Rhinol Laryngol 108:1999

SELECTIVE LARYNGEAL ADDUCTOR DENERVATION-REINNERVATION: A NEW SURGICAL TREATMENT FOR ADDUCTOR SPASMODIC DYSPHONIA

GERALD S. BERKE, MD KEITH E. BLACKWELL, MD BRUCE R. GERRATT, PHD
ANDREW VERNEIL, MD KATHERINE S. JACKSON, RN JOEL A. SERCARZ, MD
LOS ANGELES, CALIFORNIA

During the past decade, botulinum toxin (Botox) has emerged as the accepted treatment for adductor spasmodic dysphonia (ASD). This therapy, which produces bilateral weakness of the thyroarytenoid muscle, undoubtedly produces physiologic effects that are beneficial to patients with ASD. However, it also has important limitations, including the need for repeated injections, the unpredictable relationship between dosage and response, and the possibility of short-term swallowing and voice problems. In this study, we will report our preliminary experience with a new surgical treatment for ASD. In this new procedure, the adductor branch of the recurrent laryngeal nerve is selectively denervated bilaterally, and its distal nerve stumps are reinnervated with branches of the ansa cervicalis nerve. Each of the patients was followed for at least 12 months; the median follow-up is 36 months. The outcome of the operation in 21 consecutive patients is reported. Nineteen of the 21 patients were judged to have an overall severity of dysphonia that was "absent to mild" following the procedure. Only 1 patient underwent further treatment with Botox postoperatively. The implications of this new procedure for ASD are discussed.

KEY WORDS — adductor spasmodic dysphonia, laryngeal reinnervation, laryngeal surgery, thyroarytenoid muscle.

INTRODUCTION

Selective paralysis of the thyroarytenoid (TA) muscle produces favorable physiologic changes and dramatic improvement in the voices of patients with adductor spasmodic dysphonia (ASD). This has been demonstrated by the use of botulinum toxin (Botox) injected into the TA muscle as the standard treatment of choice for ASD. This report describes a new surgical treatment that produces TA and lateral cricoarytenoid (LCA) muscle paralysis in patients with ASD by selectively denervating the recurrent laryngeal nerve (RLN) branches to these muscles. In order to prevent unwanted reinnervation by RLN efferents and preserve muscle tone, the TA nerve branch is reinnervated with a branch of the ansa cervicalis. This procedure is a potential long-term surgical solution for patients who desire an alternative to repeated Botox injections.

Surgical treatments for ASD have been rejected because of the lack of long-term success. The first widely accepted treatment for ASD was RLN section, a procedure that was initially embraced by laryngologists.[1] In theory, the creation of a unilaterally paralyzed larynx could prevent vocal fold hyperadduction, at the likely cost of a breathy voice and other typical sequelae of unilateral vocal fold paralysis. Intermediate follow-up on 306 patients[2] showed self-reported recurrent ASD symptoms in only 10% to 15% of patients. Ninety percent of patients considered the operation satisfactory, and would recommend RLN section to others with ASD.

However, another study, by Aronson and DeSanto,[3] indicated that expert listeners judged that only 36% of patients were still improved after 3 years, and few laryngologists continue to treat ASD patients with RLN section. Failure of the procedure to provide long-term relief of dysphonia was attributed to persistent hyperadduction of the TA muscle in the remaining innervated hemilarynx. However, reinnervation by proximal RLN axon regrowth has also been reported on the basis of electromyography (EMG) data.[4]

Blitzer et al[5] introduced Botox as a treatment for ASD. Most laryngologists agree that paralysis of the TA muscle (as provided by Botox) is an effective method of reversing the halting speech and strained voice associated with ASD. Speech of ASD patients is often dysfluent, because the pulmonary expiratory pressure is frequently too low to overcome unpredictable moment-to-moment changes in intralaryngeal stiffness. This results in phonation that is difficult to sustain at normal conversational intensity lev-

---

From the Division of Head and Neck Surgery, University of California Los Angeles (UCLA) School of Medicine, Los Angeles (all authors), and the West Los Angeles Veteran's Affairs Medical Center (Dr Blackwell; VA Merit Review Grant #0001), Los Angeles, California.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, May 9-10, 1998.

CORRESPONDENCE — Gerald S. Berke, MD, Division of Head and Neck Surgery, UCLA School of Medicine, 10833 Le Conte Ave, Room 62-132, Los Angeles, CA 90095.

TABLE 1. PATIENTS' REASONS FOR SEEKING SURGICAL INTERVENTION

	No. of Patients
Wanted long-lasting treatment; disliked injections	8
Botox was becoming less effective	6
Botox was ineffective	2
Botox produced excessive breathiness	2
Patient had antibodies to Botox	1
Effect of Botox was too short	1
Anaphylactic reaction to Botox	1

els, and is often interrupted intermittently with voice arrests as the adductory force of the vocal folds overcomes subglottic pressure. Ludlow et al[6] reported that symptom reduction in ASD occurred when there was a reduction in TA muscle activation, and EMG recordings made following Botox administration verified the denervation of the TA muscle.[7] By paralyzing the TA muscle, Botox injection also increases airflow to normal, reduces laryngeal resistance, and produces improvements in acoustic measures, including jitter, shimmer, and signal-to-noise ratio, in ASD patients.[8,9]

The TA muscle has a profound influence on laryngeal biomechanics and voice. The muscle forms much of the bulk of the vocal fold, and therefore, its contraction has a greater impact on airway resistance than that of any other intrinsic laryngeal muscle, particularly during laryngeal adduction. Laryngeal hyperadduction is associated with forceful TA contraction, and studies have linked TA hyperactivity to symptoms in ASD.[10-12] The TA muscle also has a critical role in determining the elastic modulus of the vocal fold, which is directly related to vocal fold stiffness. An abnormally high level of this property allows the development of excessive intraglottic pressures, as seen in ASD.[13,14]

Although Botox injection produces desirable physiologic effects, it has several important limitations. The duration of Botox action is measured in months, and some patients require reinjection several times per year. Voice quality does not improve immediately upon injection, and improvement may be preceded by severe breathiness. Occasionally, patients may experience temporary dysphagia. Finally, the dose-response curve for Botox can vary greatly between individuals.

Currently, there is no ideal, long-term treatment for ASD. For patients who are satisfied with its results, Botox therapy will probably continue to be the treatment of choice in ASD. However, repeated injection is not satisfactory for every patient. For example, several of the patients in this series lived far from a medical center where Botox was available.

The procedure discussed in this report was first studied in a canine model of phonation.[15] It was found that animals did not develop high subglottic pressure with electrical overstimulation of the RLN. After further cadaver dissection, it was decided in 1993 to begin the operation in humans.

The success of previous surgical approaches for ASD has been limited, because dysphonia recurred after long-term follow-up.[3] In this study, patients have been followed longitudinally for up to 5 years to determine whether the present approach provides long-lasting relief from symptoms.

PATIENTS AND METHODS

Patients. Each of the patients had a previous diagnosis of spasmodic dysphonia that was verified by a speech scientist (B.R.G.) and the senior laryngologist (G.S.B.). All but 1 of the patients had undergone at least 1 previous injection with Botox. Patients were excluded from the series if there was less than 1 year of follow-up after the surgery or if they were unavailable for postoperative assessment. Twenty-one patients were selected who fit the criteria and form the basis for this report. Ten of the patients were male, 11 female. The median follow-up period was 36 months; the mean follow-up period was 31.4 months (range 12 to 68 months). The patients' reasons for seeking surgical intervention are listed in Table 1.

Surgical Technique. The patient was intubated with a size 6 or smaller endotracheal tube, and the neck was explored via a low transverse incision. The strap muscles were retracted laterally to expose the thyroid lamina. The inferior pharyngeal constrictor muscle was divided, if necessary, to gain access to the posteroinferior portion of the lamina. The external branch of the superior laryngeal nerve was identified and preserved.

An approximately 14 × 18-mm, inferiorly based window was made in the thyroid lamina as a cartilaginous flap. The superior border was made parallel to the lower border of the thyroid lamina, midway between the upper and lower borders of the thyroid lamina. The anterior edge of the window was immediately anterior to the inferior tubercle of the thyroid lamina. The posterior border was made just anterior to the inferior cornu. The inner perichondrium was incised and the intralaryngeal musculature gently dissected with a hemostat. The distal portion of the anterior branch of the RLN was identified and followed distally. The identity of the terminal branch was verified by stimulating the nerve with a 0.5-mA DC stimulation from a portable nerve stimulator.

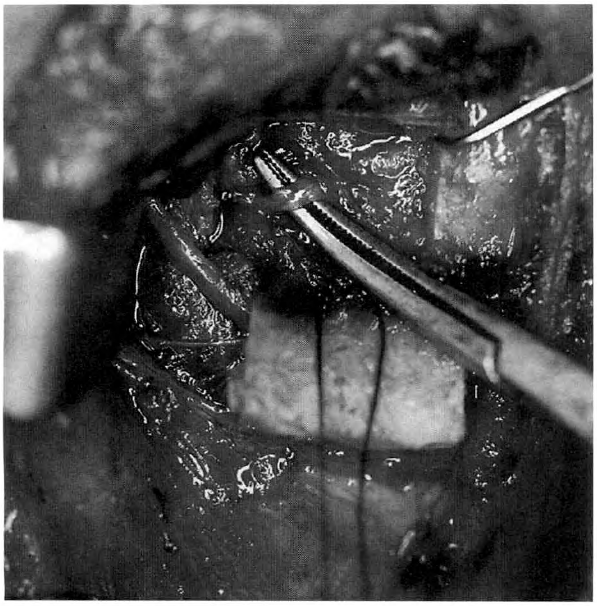


Fig 1. Left thyroarytenoid nerve is exposed through inferiorly based window in thyroid lamina.

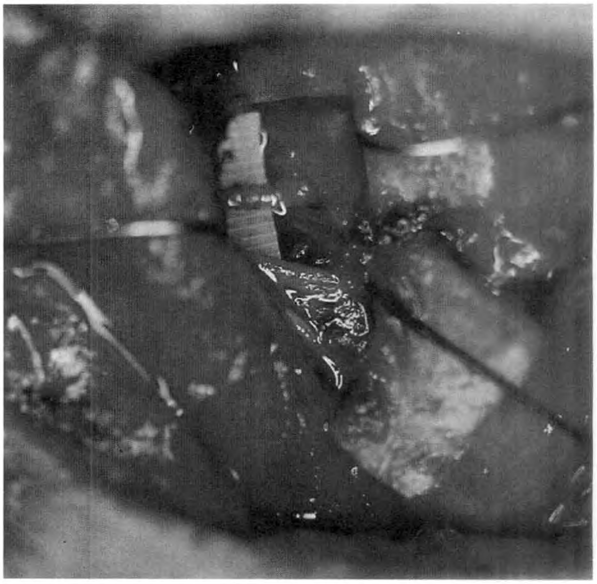


Fig 2. Left thyroarytenoid nerve following anastomosis of ansa cervicalis branch to distal branch of left thyroarytenoid nerve.

When available in the later cases in the series, evoked EMG was performed by using an electrode endotracheal tube while stimulating the TA nerve branch. This technique has been described previously by Mermelstein et al.[16]

The TA branch is located beneath the perichondrium (Fig 1). Encased in fat, it typically runs from the posteroinferior portion of the window anterosuperiorly. It occasionally lies in a deeper plane beneath the lateral fibers of the TA muscle. The TA branch of the RLN was ligated 3 mm from its termination and sectioned with a scalpel prior to its arborization into multiple branches within the muscle. The ansa cervicalis nerve was identified and an appropriately sized nerve branch selected. Generally, the sternohyoid branch of the nerve is appropriately sized for TA reinnervation. The ansa was sutured to the TA nerve with a series of interrupted sutures of 10-0 nylon (Fig 2). The proximal stump of the TA nerve branch was ligated with a 2-0 silk suture and sutured outside the cartilage window to the posterior lamina. A 2 × 2-mm (approximately) piece of thyroid cartilage was removed from the window to avoid pressure-induced injury to the ansa cervicalis nerve where it entered into the thyroid lamina window. The window was replaced and sutured to the outer perichondrium with 4-0 nonabsorbable suture.

In the last 6 patients, in addition to TA denervation-reinnervation, nerve fibers destined for the LCA muscle were identified and sectioned to provide maximal reduction of adductory force. The LCA branch of the nerve was identified by following the RLN proximally until the nerve branch directed toward the LCA muscle was identified. Then the LCA branch was sectioned sharply, and there was no attempt to reinnervate the LCA branch.

The strap muscles were reapproximated in the midline. The platysma and skin were closed in layers. A flexible drain was kept in the wound overnight. The patients were observed in the hospital until they could tolerate an oral diet and any airway edema had subsided.

Expert Voice Assessment. A senior speech scientist with at least 10 years of experience evaluating voices rated each patient on the basis of 5 speech characteristics both before and after the surgery. The preoperative assessment was based on the voice findings made before treatment with Botox. For each category, the voice was rated on a scale of 1 (absent to mild), 2 (mild to moderate), or 3 (moderate to severe). The surgeon was excluded from providing the ratings.

Questionnaire. A telephone survey was used to obtain patient opinion about the outcome of the procedure. Each patient was asked a series of questions and asked to respond on a scale from 1 to 5. Patients were asked a series of questions over the telephone. Of the 21 patients in the series, 1 could not be contacted by telephone for completion of the questionnaire, but was included in the series because he was seen frequently postoperatively for more than 3 years.

RESULTS

Patient and Expert Assessment. The results of the telephone survey are listed in Table 2. Each score

TABLE 2. QUESTIONNAIRE GIVEN TO EACH PATIENT IN TELEPHONE INTERVIEW

	Average Score
I would recommend this operation to others with spasmodic dysphonia.	4.58
My speech is more fluent after the surgery.	4.53
My speech is better following surgery than following Botox.	4.50
I am not embarrassed speaking in public.	4.53
My speech is understandable.	4.53
Botox treated my spasmodic dysphonia successfully.	2.94
My speech problems with spasmodic dysphonia have not returned following surgery.	4.05

1 — strongly disagree; 5 — strongly agree.

indicated is the mean response for each question. There was strong agreement with 6 of the 7 statements indicating successful outcome following the procedure. The results of the expert assessment are summarized in Table 3. In general, patients had moderate to severe dysphonia prior to the operation and mild voice symptoms postoperatively.

Surgical Outcome and Further Treatment. No patients experienced airway compromise postoperatively, despite bilateral denervation. All patients experienced severe vocal fold bowing and breathiness in the early postoperative period. This normalized after 3 to 6 months, presumably when the ansa cervicalis reinnervation occurred. Patients were instructed to maintain a dysphagia diet in the week following the surgery.

The surgical morbidity is reported in Table 4. There was 1 serious complication of the procedure, in a patient who developed aspiration pneumonia postoperatively and required hospitalization. The degree of postoperative breathiness is not listed in Table 4, because this finding was consistent with the goal of the procedure.

TABLE 3. SPEECH SCIENTIST RANKINGS OF VOCAL FINDING SEVERITY BEFORE AND AFTER SURGERY

		No. of Patients		
Speech Finding		*Absent to Mild*	*Mild to Moderate*	*Moderate to Severe*
Overall severity of dysphonia	Before	0	8	13
	After	19	2	0
Strained voice quality	Before	0	13	8
	After	18	3	0
Voice breaks	Before	0	5	16
	After	19	2	0
Dysfluency	Before	0	7	14
	After	17	4	0

TABLE 4. SURGICAL MORBIDITY

	No. of Patients
Temporary aspiration (>2 wk)	2
Glottal insufficiency	2
Vocal fold granuloma	1
Wound seroma	1

The additional treatment is listed in Table 5. Only 1 patient has undergone Botox therapy postoperatively. Botox has remained effective in this individual. One patient underwent collagen injection to lessen a vocal fold tremor that was unmasked following TA denervation. Her speech was otherwise without dystonia. One patient underwent successful TA myotomy following aberrant reinnervation with the sectioned RLN. Her voice is slightly harsh but fluent, and the patient is quite satisfied. One patient continues with voice therapy to strengthen her voice.

DISCUSSION

The results presented in this study strongly support the need for further investigation of the role of selective bilateral RLN denervation in ASD treatment. Although the technique must be studied in a larger group of patients with objective measures of phonation, there is room for some optimism for patients seeking an alternative to Botox therapy.

The selective denervation presented in this study appears to have permanent effects similar to the short-term effects of TA Botox injection. This technique is successful, because it prevents the elevated intraglottic (and, secondarily, subglottic) pressures produced in patients with ASD. This prediction is consistent with experience in humans with TA Botox therapy.

Our preliminary results in 21 patients followed for a mean of 3 years indicate that selective bilateral RLN denervation with ansa reinnervation will be less prone to failure than total RLN section. It will take long-term follow-up in a large series of patients to verify this expectation, however. Ansa cervicalis TA reinnervation should prevent unwanted reinnervation from other proximal RLN efferents, a problem that limited the effectiveness of RLN section.[4] Experience with ansa reinnervation of the RLN for laryngeal paralysis indicates that purposeful adduction is not achieved.[17]

TABLE 5. ADDITIONAL TREATMENT

	No. of Patients
Collagen injection	1
Thyroarytenoid myotomy	1
Botulinum toxin treatment	1
Voice therapy	1

The ansa reinnervation nerve provides tone to the TA muscle and lessens the problems with breathiness that plague many Botox patients shortly after injection. Further, the preservation of the interarytenoid muscle allows posterior closure of the glottis to avoid some of the difficulties experienced with whole nerve section of the RLN.

Because of the critical role of the TA muscle in producing the elevated intralaryngeal pressures in ASD, the first 15 patients in the series underwent TA denervation alone. The senior author (G.S.B.) modified the procedure to divide some nerve fibers destined for the LCA muscle to maximize the effect of the operation. Although there is theoretic concern about loss of vocal fold adduction after denervation of the 2 strongest laryngeal adductors, there has not been loss of adduction in any of the 6 patients that have had denervation of both the LCA and TA muscles.

There are several possible problems with the selective denervation procedure proposed in this study. One potential complication is injury to proximal branches of the RLN, particularly the posterior cricoarytenoid (PCA) branch. This is unlikely to occur, because the thyroid cartilage window does not expose the PCA branch in most larynges. Also, because of the direction of the PCA nerve (directed more posteriorly), it is unlikely that a surgeon familiar with normal RLN anatomy would injure the PCA branch. Nonetheless, as the operation is somewhat difficult to perform, it should be first attempted in cadaver larynges. Although changes in vocal quality do occur following the procedure, these effects seem to be less than with Botox treatment. Most patients have normal conversational speech intensity with good inflection and no signs of breathiness. Denervation of the TA muscle reduces fine motor control of the larynx, and the pitch and loudness range of patients is mildly restricted following selective denervation. This occurs because the TA muscle functions in pitch and loudness control, and contracts forcefully during loud phonation and while singing at the higher frequencies. Swallowing problems such as aspiration occurred in 2 patients, but have not been long-lasting, because the closure and sensation of the larynx are not affected. Because the procedure creates a permanent alteration in laryngeal function, it should be performed only in patients with relatively severe symptoms.

In summary, the proposed procedure provides an alternative to Botox with sustained and beneficial effects. Only careful ongoing analysis of results, with adequate follow-up, can determine whether this promise will be fulfilled.

REFERENCES

1. Dedo HH. Recurrent nerve section for spastic dysphonia. Ann Otol Rhinol Laryngol 1976;85:451-9.

2. Dedo HL, Izdebski K. Problems with surgical (RLN section) treatment of spastic dysphonia. Laryngoscope 1983;93: 268-71.

3. Aronson AE, DeSanto LW. Adductor spasmodic dysphonia: three years after recurrent nerve section. Laryngoscope 1983;93:1-8.

4. Fritzell B, Feuer E, Haglund S, Knutsson E, Schiratzki H. Experiences with recurrent laryngeal nerve section for spastic dysphonia. Folia Phoniatr (Basel) 1982;34:160-7.

5. Blitzer A, Brin MF, Fahn S, Lange D, Lovelace RE. Botulinum toxin for the treatment of spastic dysphonia. Laryngoscope 1986;96:1300-1.

6. Ludlow C, Baker M, Naunton R, Hallett M. Intrinsic muscle activation in spasmodic dysphonia. In: Benecke R, Conrad B, Marsden CD, eds. Motor disturbances: a selection of papers delivered at the 1st Congress of the International Medical Society of Motor Disturbances held at Lausanne, Switzerland, 19-21 June, 1986. San Diego, Calif: Academic Press, 1987:119-30.

7. Brin MF, Blitzer A, Fahn S, Gould W, Lovelace RE. Adductor laryngeal dystonia (spastic dysphonia): treatment with local injections of botulinum toxin (Botox). Mov Disord 1989; 4:287-96.

8. Zwirner P, Murry T, Swenson M, Woodson GE. Effects of botulinum toxin therapy in patients with adductor spasmodic dysphonia: acoustic, aerodynamic and videoendoscopic findings. Laryngoscope 1992;102:400-6.

9. Adams SG, Durkin LC, Irish JC, Wong DLH, Hunt EJ. Effects of botulinum toxin type A injections on aerodynamic measures of spasmodic dysphonia. Laryngoscope 1996;106: 296-300.

10. Ludlow CL, Naunton RF, Sedory SE, Schultz GM, Hallett M. Effects of botulinum toxin injections on speech in adductor spasmodic dysphonia. Neurology 1988;38:1220-5.

11. Shipp T, Izdebski K, Reed C, Morrissey P. Intrinsic laryngeal muscle activity in a spastic dysphonic patient. J Speech Hear Disord 1985;50:54-9.

12. Nash EA, Ludlow CL. Laryngeal muscle activity during speech breaks in adductor spasmodic dysphonia. Laryngoscope 1996;106:484-9.

13. Fujimura O. Body-cover theory of the vocal fold and its phonetic implications. In: Stevens KN, Hirano M, eds. Vocal fold physiology. Tokyo, Japan: University of Tokyo Press, 1981: 271-88.

14. Berke GS, Gerratt BR. Laryngeal biomechanics: an overview of mucosal wave mechanics. J Voice 1993;7:123-8.

15. Sercarz JA, Berke GS, Ming Y, Rothschiller J, Graves MC. Bilateral thyroarytenoid denervation: a new treatment for laryngeal hyperadduction disorders studied in the canine. Otolaryngol Head Neck Surg 1992;107:657-68.

16. Mermelstein M, Nonweiler R, Rubinstein EH. Intraoperative identification of laryngeal nerves with laryngeal electromyography. Laryngoscope 1996;106:752-6.

17. Zheng H, Li Z, Zhou S, Cuan Y, Wen W. Update: laryngeal reinnervation for unilateral vocal cord paralysis with the ansa cervicalis. Laryngoscope 1996;106:1522-7.

Ann Otol Rhinol Laryngol 108:1999

MORPHOLOGY OF THE HUMAN LARYNX DURING THE FIRST FIVE YEARS OF LIFE STUDIED ON WHOLE ORGAN SERIAL SECTIONS

HANS EDMUND ECKEL, MD
COLOGNE, GERMANY

JUERGEN KOEBKE, PHD
COLOGNE, GERMANY

CHRISTIAN SITTEL, MD
COLOGNE, GERMANY

GEORG MATHIAS SPRINZL, MD
INNSBRUCK, AUSTRIA

CLAUS POTOTSCHNIG, MD
INNSBRUCK, AUSTRIA

EBERHARD STENNERT, MD
COLOGNE, GERMANY

The morphologic development of the human larynx during the first years of life is poorly understood to date. This study used plastinated whole organ serial sections to determine the growth and structure of the infant larynx. The larynges of 43 children 1 to 60 months old were plastinated. Whole organ serial sections were obtained by cutting the resulting specimen with a diamond band saw. The slices were then submitted to computer-assisted morphometric investigation. We found that the subglottic airway rapidly increases in size during the first 2 years of life. Further growth follows a linear mode. The relative proportion of the mucosal lining decreases likewise. In contrast to that in adults, and comparable to that in most mammals, the cartilaginous glottis accounts for 60% to 75% of the vocal folds' length at <2 years. No sexual dimorphism of the larynx exists during childhood. This study supplies detailed morphometric data on the growth and structure of the human larynx during the first years of life. It is the first to use plastinated whole organ serial sections for morphology of the pediatric larynx. Therefore, this study provides quantitative anatomic data of clinical interest that have not been available to date.

KEY WORDS — laryngeal anatomy, laryngeal growth, pediatric airway, plastination, subglottic anatomy, vocal cord anatomy.

INTRODUCTION

The embryology of the human larynx and its development during infancy was first studied during the first half of this century.[1,2] The material of the Carnegie Collection of human embryos, first started at Johns Hopkins University in 1887, has provided detailed information on the embryonic development of the larynx, including detailed morphometric data.[3-8] However, the morphologic development of the human larynx during the fetal period and the first years of life has not been studied as extensively and has mainly been described on a qualitative basis.[9-13] This study used plastinated whole organ serial sections to determine the growth and structure of the infant larynx. Whole organ serial sections have demonstrated their outstanding value as a major research tool for the study of laryngeal morphology.[14] They have previously been used to study the details of infant larynx development.[15-17] The application of the plastination technique to whole organ serial sectioning of the larynx has been demonstrated to provide slides with computable shrinkage artifacts.[18] Therefore, this technique seems suitable for the study of morphologic details on serial sections of the larynx.

This study seeks to provide the detailed morphometric data on the regular anatomy of the vocal cords, the subglottic airway, and the tracheal airway dimensions gained from plastinated whole organ serial sections of 43 larynges and to determine morphologic changes with age. Such information may be useful for the understanding of pediatric airway disease or for laryngeal surgery in children.[19,20]

MATERIAL AND METHODS

The data for this study were obtained from 43 autopsy specimens at the Institute of Legal Medicine of the University of Cologne. The larynges were removed on the occasion of routine autopsies 12 to 48 hours postmortem. If tumors or traumatic lesions of the larynx became evident during autopsy, or if a history of previous tracheal intubation was reported, the larynges were excluded from this investigation. Twenty-three of the deceased children were male, and 20 were female. The birth date was available in all cases, but the gestational age was not. No clinical data, except for the date of birth and the sex of the children, were available for this study for data protection reasons. Therefore, data on the causes of death for the study population cannot be given in this article, although these data would have been of importance with respect to understanding the findings presented in this study. The age distribution of the study population is given in Fig 1.

From the Departments of Otorhinolaryngology (Eckel, Sittel, Stennert) and Anatomy (Koebke), University of Cologne, Cologne, Germany, and the Department of Otorhinolaryngology, University of Innsbruck, Innsbruck, Austria (Sprinzl, Pototschnig). This study was supported by a grant from Jean-Uhrmacher-Stiftung, Cologne, Germany.

Presented at the meeting of the American Laryngological Association, Scottsdale, Arizona, May 10-11, 1997.

CORRESPONDENCE — Hans Edmund Eckel, MD, Univ. HNO Klinik, 50924 Koeln, Germany.

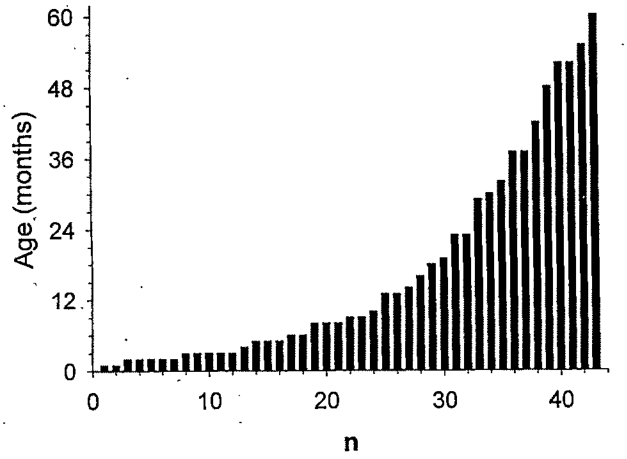


Fig 1. Age distribution (n = 43).

During autopsy, the larynx was removed in continuity with the lung, trachea, thyroid gland, and tongue. Prior to any measurements, the larynx had to be freed of these adjacent structures. Some of the specimens had been opened through the plate of the cricoid cartilage and needed readaptation prior to further processing.

Block Plastination. All larynges were embedded as whole organs. Dehydration was accomplished by freeze substitution in precooled acetone (technical grade) at –23°C over 2 weeks, with acetone being renewed weekly. This procedure was followed by a bath of methylene chloride for 4 days, with solution being renewed twice.

The larynx was then taken out of the methylene chloride and put into the resin mixture[18] for the actual plastination (Biodur products, D-69126 Heidelberg, Germany). The specimens were then put into a vacuum chamber for about 2 weeks. Methylene chloride, with its high vapor pressure and its low boiling point, is extracted continuously in the form of gas bubbles, while the polymer solution, with its low vapor pressure and high boiling point, is forced into the specimen (hence the term forced impregnation). Final hardening was achieved by heat treatment at 60°C.

The resulting resin blocks were trimmed to an appropriate size and cut on a diamond wire saw to a section thickness of about 0.8 mm. Cutting loss per section is 0.22 mm with this method. To improve transparency, specimens were polished, stained, and embedded as previously described.[21]

Computer-Aided Morphometry. Morphometry of whole organ sections was accomplished with a high-resolution, computer-based image analyzer as previously described.[21] The system consists of a high-performance tripod camera mounted above a light source, an additional movable ring light with a cold light supply, a personal computer with a mathematical coprocessor, a special video slot card, 2 monitors, a digitalizing tablet with a 4-button mouse as an input device, and matching image analyzer software.

The total length of the glottis, length of the cartilaginous and ligamentous glottis, subglottic cartilaginous cross section, subglottic airway, and tracheal airway were determined for each specimen.

Statistical Methods. Mean values with standard deviation and standard error and minimum and maximum values as displayed in the Table were calculated with Sigma Plot Software Version 3 (Jandel Scientific Software, San Rafael, Calif). The scatter plots that demonstrate the results of this study were also generated with this software.

RESULTS

The results of the morphometric investigation conducted in this study are summarized in the Table. Figure 2 demonstrates the allocation of individual morphometric measurements according to age. Figure 3 gives examples of whole organ serial sections and specifies the normal anatomy of the pediatric larynx. The subglottic airway increases considerably in size during the first 2 years of life (mean, from 13 to 28 mm^2; Fig 2C). Further growth seems to follow a linear mode. The relative proportion of the mucosal lining of the subglottic airway decreases likewise. While it occupies approximately 50% of the subglottic cartilaginous cross section during the first 2 years of age, its relative proportion decreases to some 30% to 40% between ages 3 and 5. In contrast to that in adults, and comparable to that in most mammals, the cartilaginous glottis accounts for 60% to 75% of the vocal folds' length in children under 2 years of age. The anterior, ligamentous part of the glottis grows larger than the posterior, cartilaginous portion during the third year of life (Fig 2B). As in adults, the subglottic airway is consistently narrower than the tracheal airway. The supraglottic structures are characterized by a large amount of submucous glands and loose connective tissue relative to the supraglottic airway (Fig 3A,B). As expected, a wide interindividual variation was found between measurements. No sexual dimorphism of the larynx was found in this study (see Table).

DISCUSSION

Whole organ serial sections of the human larynx play an important role in the assessment of normal and pathologic anatomy in experimental laryngology.[16-18,22] Due to the complex anatomy of the hu-

MORPHOMETRIC DATA FROM 43 INFANT LARYNGES

		Length of Glottis (mm)	*Length of Cartilaginous Glottis (mm)*	*Length of Ligamentous Glottis (mm)*	*Subglottic Cartilaginous Cross Section (mm²)*	*Subglottic Airway (mm²)*	*Tracheal Airway (mm²)*
Male, 0-24 mo (n = 19)	Mean	7.2	4.6	2.7	32.6	16.8	17.9
	SD	1.1	0.7	0.8	9.6	4.6	4.6
	SE	0.3	0.2	0.2	2.2	1.0	1.1
	Minimum	5.2	3.4	1.7	18.1	10.8	13.7
	Maximum	9.5	6.4	4.6	49.7	25.3	29.3
Female, 0-24 mo (n = 13)	Mean	7.2	4.0	3.1	38.2	20.8	22.3
	SD	1.0	0.9	1.0	9.8	6.7	7.8
	SE	0.3	0.3	0.3	2.7	1.9	2.3
	Minimum	5.8	2.8	1.4	22.4	12.5	13.2
	Maximum	9.2	5.9	4.9	51.3	34.5	37.7
Male, 25-60 mo (n = 4)	Mean	10.3	4.6	5.7	56.3	35.6	43.6
	SD	1.6	0.9	0.8	9.2	10.3	11.8
	SE	0.8	0.5	0.4	4.6	5.1	5.9
	Minimum	8.3	3.2	5.1	44.2	26.0	26.2
	Maximum	12.2	5.3	6.9	66.4	49.4	51.5
Female, 25-60 mo (n = 7)	Mean	9.6	4.7	4.8	54.5	37.4	39.4
	SD	1.3	0.4	1.2	8.0	5.9	6.2
	SE	0.5	0.1	0.5	3.0	2.2	2.4
	Minimum	8.2	4.2	3.4	46.5	30.1	32.4
	Maximum	11.8	5.2	6.7	68.5	46.5	50.8

man larynx, which contains different types of tissue with marked differences in hardness, the production of high-quality serial sections can be difficult to accomplish. Conventional laboratory techniques have previously been used for the qualitative morphology of the larynx and study of related pathologic changes. However, these well-established methods show serious drawbacks in certain respects. These procedures are based either on celloidin or parafffin embedding. The first requires a 6-month processing time and expensive material, and the resulting specimens are invariably too thick for histologic investigation. The latter allows for faster processing, but the final cutting of specimens frequently creates artifacts. Prior decalcification is mandatory for both techniques.[21]

The technique of plastination was first described by von Hagens[23] in 1979. It entails the replacement of water and lipids in tissues by curable polymer on a cellular level. The procedure consists of 4 steps: fixation, dehydration, forced impregnation in a vacuum, and hardening. The process has previously been described in detail.[18,23,24] The resulting specimens are dry and odorless and do not deteriorate with time. Block plastination provides macroscopic organ slices of high quality in a reasonable amount of time and at reasonable cost. The degree of tissue alteration and shrinkage encountered with the plastination of human larynges has previously been described in detail.[18] Therefore, this technique is perfectly suitable for nonhistologic morphometry on a great number of specimens and has the potential to provide slides that can be submitted to morphometric evaluation.

Previous studies on the anatomic configuration of the infant larynx have focused on the perinatal larynx,[17,25] the prepubertal and pubertal larynx,[26,27] and the development of collagen fibers in the developing larynx.[15,16,28] Pracy[10] used graduated endotracheal tubes to determine the narrowest subglottic airway diameter. Sellars and Keen[12] and Too-Chung and Green[29] have provided data from anatomic measurements of unprocessed infant larynges gained with vernier calipers. Their investigations focused mainly on the development of the cricoid cartilage. With this method, an accurate assessment of the glottic structures is difficult and frequently even impossible.[30] Tucker et al,[17] in 1977, conducted a study on whole organ serial sections of neonate larynges and were the first to describe the V-shaped configuration of the posterior cricoid lamina.

The human larynx has undergone significant evolutionary adaptations.[31] Among them are the descent

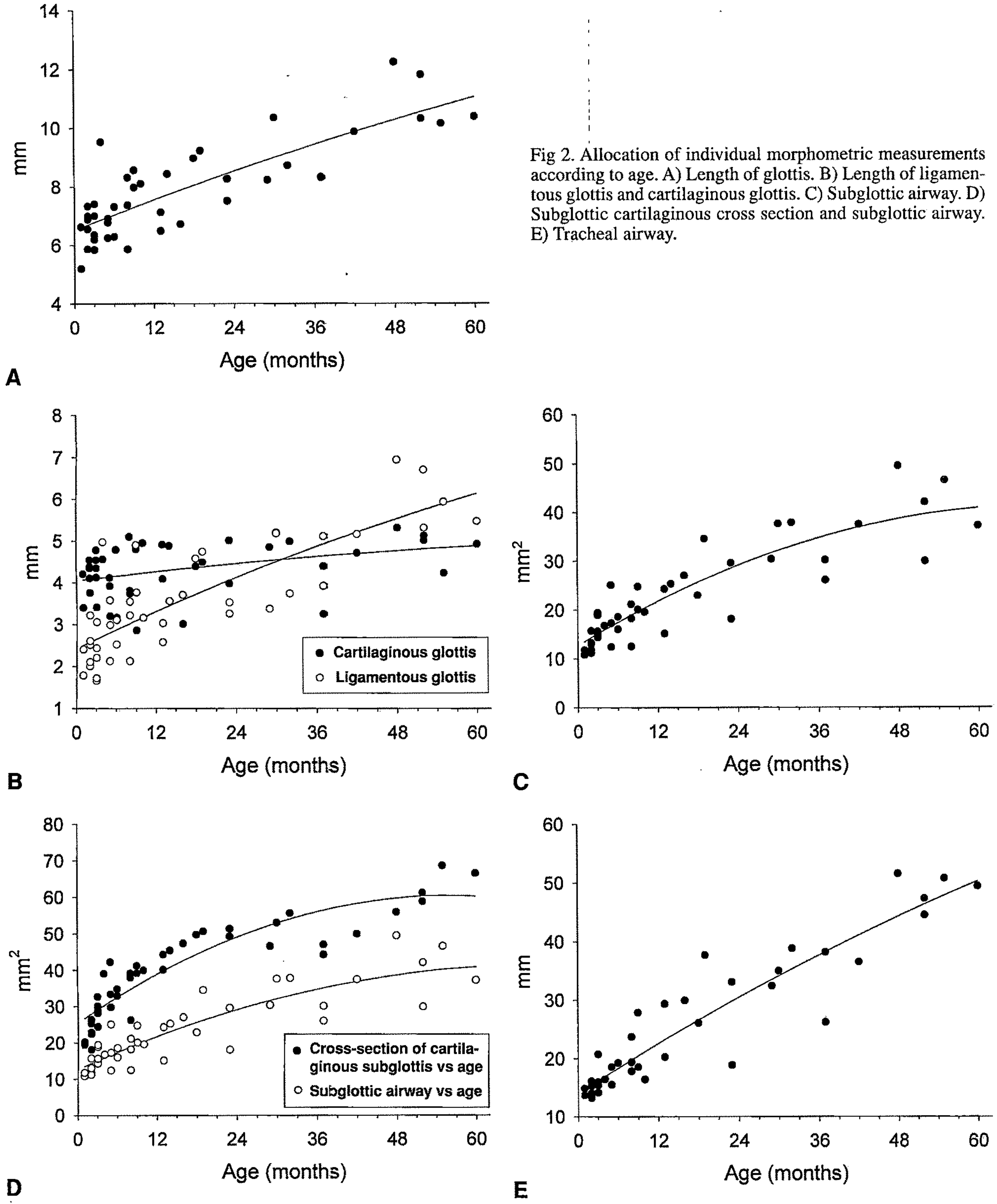


Fig 2. Allocation of individual morphometric measurements according to age. A) Length of glottis. B) Length of ligamentous glottis and cartilaginous glottis. C) Subglottic airway. D) Subglottic cartilaginous cross section and subglottic airway. E) Tracheal airway.

of the larynx, the capability of vocal fold adjustment in length, tension, and shape, and the prominent configuration of the membranous part of the vocal folds as opposed to the cartilaginous part. The infant larynx is not just a miniature of the adult organ.[15] It shows differences in its position relative to the vertebral column, in the composition of cartilages and soft tissues, and in environmental adaptation. The present study is the first to supply detailed morphometric data on the growth and structure of the human larynx during the first 5 years of life and on the morphologic changes of the larynx during this pe-

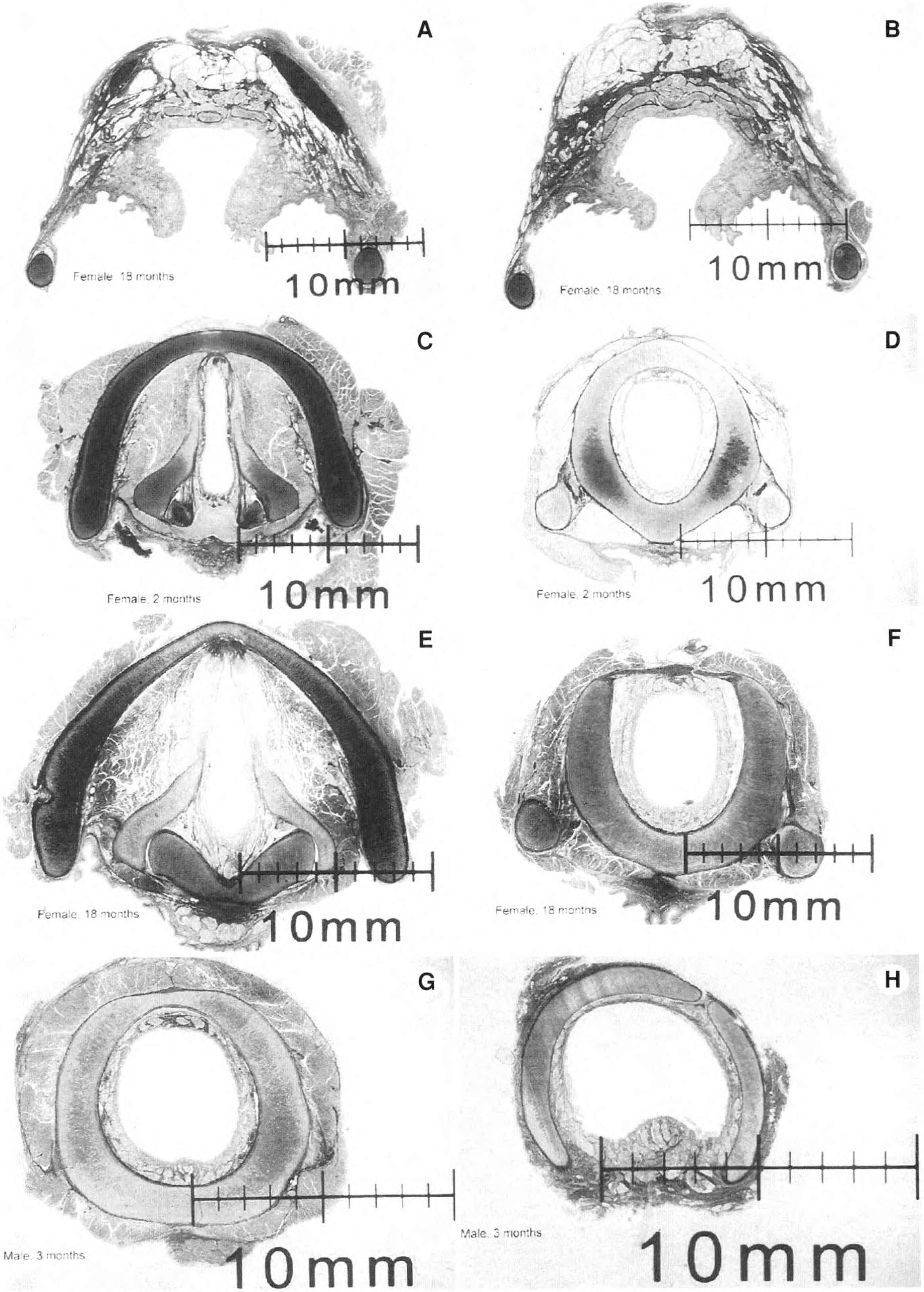


Fig 3. Examples of whole organ serial (transverse) sections. A) Through supraglottis at superior margin of thyroid cartilage of 18-month-old girl. B) Through supraglottis above thyroid cartilage in same specimen as in A. C) Through glottis of 2-month-old girl. D) Through subglottis in same specimen as in C. E) Through glottis of 18-month-old girl. F) Through subglottis at cricothyroid membrane in same specimen as in E. G) Through subglottis of 3-month-old boy. H) Through second tracheal ring in same specimen as in G.

riod. From these data it seems that some of the adaptations of the human larynx, as opposed to those of other vertebrates, are not fully developed at birth, but undergo postnatal maturation. The relative proportions of the cartilaginous and membranous parts of the vocal folds clearly demonstrate this maturation process: while the posterior "respiratory" glottis accounts for some 60% to 75% of the total glottic length in newborns, its relative proportion decreases throughout the first years of life and finally equals that of the adult larynx (ie, 30% to 45%[22,32]). In contrast to adults,[30] and in accordance with the literature,[27] no sexual dimorphism of the larynx could be detected in this series of infant larynges.

CONCLUSION

This study supplies detailed morphometric data on the growth and structure of the human larynx during the first years of life. It is the first to use plastinated whole organ serial sections for pediatric laryngeal morphology. Therefore, this study provides quantitative anatomic data of clinical interest that have not been available to date.

ACKNOWLEDGMENTS — The authors are grateful to Sabine Ricke for processing the specimens and for the photography used in this article, and to Gregor Held, who helped to prepare the plastinated specimens at the Larynx Morphology Research Laboratory, Department of Otorhinolaryngology, University of Cologne.

REFERENCES

1. Frazer JE. The development of the larynx. J Anat Physiol 1910;44:156-91.

2. Lisser H. Studies on the development of the human larynx. Am J Anat 1911;12:27-66.

3. O'Rahilly R, Boyden EA. The timing and sequence of events in the development of the human respiratory system during the embryonic period proper. Z Anat Entwicklungsgesch 1973;141:237-50.

4. O'Rahilly R, Müller F. Respiratory and alimentary relations in staged human embryos. New embryological data and congenital anomalies. Ann Otol Rhinol Laryngol 1984;93:421-9.

5. O'Rahilly R, Tucker JA. The early development of the larynx in staged human embryos. Part I. Embryos of the first five weeks (to stage 15). Ann Otol Rhinol Laryngol [Suppl] 1973;82(suppl 7).

6. Müller F, O'Rahilly R, Tucker JA. The human larynx at the end of the embryonic period proper. 2. The laryngeal cavity and the innervation of its lining. Ann Otol Rhinol Laryngol 1985;94:607-17.

7. Tucker JA, Tucker GF. Some aspects of fetal laryngeal development. Ann Otol Rhinol Laryngol 1975;84:49-55.

8. Tucker JA, O'Rahilly R. Observations on the embryology of the human larynx. Ann Otol Rhinol Laryngol 1972;81:520-3.

9. Fried MP, Kelly JH, Strome M. Comparison of the adult and infant larynx. J Fam Pract 1982;15:557-8, 561.

10. Pracy R. The infant larynx. J Laryngol Otol 1983;97:933-47.

11. Sasaki CT, Levine PA, Laitman JT, Crelin ES Jr. Postnatal descent of the epiglottis in man. A preliminary report. Arch Otolaryngol 1977;103:169-71.

12. Sellars I, Keen EN. Laryngeal growth in infancy. J Laryngol Otol 1990;104:622-5.

13. Sellars SL. The enigma of the infant larynx. Clin Otolaryngol 1983;8:371-9.

14. Kirchner JA. What have whole organ sections contributed to the treatment of laryngeal cancer? Ann Otol Rhinol Laryngol 1989;98:661-7.

15. Cohen SR, Cheung DT, Nimni ME, et al. Collagen in the developing larynx. Preliminary study. Ann Otol Rhinol Laryngol 1992;101:328-32.

16. Cohen SR, Perelman N, Nimni ME, Mahnovski V, Cheung DT. Whole organ evaluation of collagen in the developing human larynx and adjoining anatomic structures (hyoid and trachea). Ann Otol Rhinol Laryngol 1993;102:655-9.

17. Tucker GF, Tucker JA, Vidic B. Anatomy and development of the cricoid. Serial-section whole organ study of perinatal larynges. Ann Otol Rhinol Laryngol 1977;86:766-9.

18. Eckel HE, Sittel C, Sprinzl G, Walger M, Koebke J. Plastination: a new approach to morphological research and instruction with excised larynges. Ann Otol Rhinol Laryngol 1993;102:660-5.

19. Bean JK, Verwoerd Verhoef HL, Verwoerd CD. Intrinsic and extrinsic factors relevant to the morphology of the growing cricoid ring after a combined anterior and posterior cricoid split: an experimental study in rabbits. Int J Pediatr Otorhinolaryngol 1994;29:129-37.

20. Sasaki CT. Development of laryngeal function: etiologic significance in the sudden infant death syndrome. Laryngoscope 1979;89:1964-82.

21. Sittel C, Eckel HE, Sprinzl GM, Stennert E. Plastination of the larynx for whole-organ sectioning. Eur Arch Otorhinolaryngol Suppl 1997;254(suppl 1):S93-S96.

22. Eckel HE, Sittel C. Morphometry of the larynx in horizontal sections. Am J Otolaryngol 1995;16:40-8.

23. von Hagens G. Impregnation of soft biological specimens with thermosetting resins and elastomers. Anat Rec 1979;194:247-55.

24. Sprinzl GM, Eckel HE, Sittel C, Thumfart WF, Koebke J. Whole organ plastination in otorhinolaryngology [Ganzorganplastination in der Hals-Nasen-Ohrenheilkunde]. HNO 1995;43:282-6.

25. Schild JA. Relationship of laryngeal dimensions to body size and gestational age in premature neonates and small infants. Laryngoscope 1984;94:1284-92.

26. Kahane JC. A morphological study of the human prepubertal and pubertal larynx. Am J Anat 1978;151:11-9.

27. Kent RD, Vorperian HK. Development of the craniofacial-oral-laryngeal anatomy. A review. San Diego, Calif: Singular Publishing Group, 1995:26-35.

28. Reidenbach MM. Normal topography of the conus elas-

ticus. Anatomical bases for the spread of laryngeal cancer. Surg Radiol Anat 1995;17:107-11.

29. Too-Chung MA, Green JR. The rate of growth of the cricoid cartilage. J Laryngol Otol 1974;88:65-70.

30. Eckel HE, Sittel C, Zorowka P, Jerke A. Dimensions of the laryngeal framework in adults. Surg Radiol Anat 1994;16:31-6.

31. Kirchner JA. The vertebrate larynx: adaptations and aberrations. Laryngoscope 1993;103:1197-201.

32. Hirano M, Kurita S, Kiyokawa K, Sato K. Posterior glottis. Morphological study in excised human larynges. Ann Otol Rhinol Laryngol 1986;95:576-81.

≈

RECENT ADVANCES IN OTITIS MEDIA

The 7th International Symposium on Recent Advances in Otitis Media will be held June 1-5, 1999, in Fort Lauderdale, Florida. For information, contact David J. Lim, MD, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057.

≈

FIFTH INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Fifth International Conference on Head and Neck Cancer will be held July 29–August 2, 2000, in San Francisco, California. For information, contact Concepts in Meetings & Events, Robin L. Wagner, President, 7819 Lloyd Ave, Pittsburgh, PA 15218-1941; telephone (412) 243-5156; fax (412) 243-5160; e-mail rlwa@med.pitt.edu.

Ann Otol Rhinol Laryngol 108:1999

HYPOGLOSSAL NERVE TRANSFER FOR LARYNGEAL REINNERVATION: A PRELIMINARY STUDY

RANDAL C. PANIELLO, MD
ST LOUIS, MISSOURI

PATTY LEE, MD
ALBUQUERQUE, NEW MEXICO

J. DAVID DAHM, MD
ST LOUIS, MISSOURI

The hypoglossal nerve is a logical donor nerve for hemilaryngeal reinnervation because 1) its activity coincides with normal laryngeal adduction during speech and deglutition; 2) it is a large nerve with many axons; and 3) donor site morbidity is low. This method of laryngeal reinnervation has not been previously reported. Previous studies using the ansa cervicalis for reinnervation have failed to show spontaneous activity. Hypoglossal-to–recurrent laryngeal nerve anastomosis was performed on a series of 5 dogs. The vocal folds were viewed monthly, with the animals awake, by infraglottic examination through a permanent tracheostomy. One dog failed due to technical error. The remaining 4 dogs began to exhibit spontaneous vocal fold adduction within 2 to 4 months. Vocal fold motion was synchronous with spontaneous tongue motion. Complete glottic closure was seen during swallowing at 3 to 5 months. Intraglottic pressure measurements following reinnervation were normal. Hypoglossal nerve transfer appears to be capable of providing functional adduction to the paralyzed hemilarynx. The potential advantages and disadvantages of this new technique are discussed.

KEY WORDS — hypoglossal nerve, laryngeal reinnervation, nerve transfer.

INTRODUCTION

The treatment of unilateral vocal fold paralysis has interested researchers for decades, yet a completely satisfactory method has been elusive. Vocal fold medialization techniques are most commonly used, including thyroplasty,[1] arytenoid adduction,[2] and injection.[3,4] While these methods provide good results for most patients, medialization methods still have some limitations due to their static nature.[5-7] The ideal treatment for unilateral vocal fold paralysis would be dynamic and would restore normal physiologic movement to the vocal fold.[8] This is most likely to require some form of laryngeal reinnervation.

The first successful laryngeal reinnervation was reported in 1909 by Horsley,[9] who described reanastomosis of a severed recurrent laryngeal nerve (RLN). Others have reported sporadic success in restoring motion by primary anastomosis or nerve grafting, but synkinesis with little or no vocal fold motion is reported most frequently.[5,6,10,11]

Fraser[12] first reported anastomosis of the ansa cervicalis to the RLN trunk in 1924, and achieved partial restoration of function. More recently, this method has been championed by Crumley[3,13] and Crumley and Izdebski,[14] who feel that maintenance of thyroarytenoid muscle tone provided by the "physiologically quiet" ansa results in a better voice, despite the lack of motion. Green et al[15] studied ansa-RLN transfer in a canine model, and found no motion except on supramaximal stimulation of the ansa graft. This group later reported further enhancement of vocal efficiency if the vocal fold was also medialized by arytenoid adduction.[16] Tucker[17] and others[18] have used a nerve-muscle pedicle based on the ansa, and found improved results when it was combined with type I thyroplasty.[19]

Crumley[3] and Crumley and Izdebski[14] report that some patients who undergo ansa-RLN anastomosis have good voice results. The lack of adductory motion in these patients makes this technique essentially another static method. This immobility is probably due to 1) synkinesis, as both adductor and abductor muscles are reinnervated,[10,20] and 2) an inadequate number of regenerated axons.[13] The relative contributions of these two factors is not known. Crumley[10] also argues that good muscle tone without motion may actually be preferable to the uncoordinated motion seen following some cases of pri-

---

From the Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine, and the John Cochran Veterans Affairs Medical Center, St Louis, Missouri. Supported by a grant from the Veterans Affairs Research Advisory Group, a National Institutes of Health Resident Training Grant, and funding from the Washington University Department of Otolaryngology–Head and Neck Surgery. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Veterans Affairs Medical Center, St Louis, Missouri.

Presented at the meeting of the American Laryngological Association, Scottsdale, Arizona, May 10-11, 1997.

CORRESPONDENCE — Randal C. Paniello, MD, 517 S Euclid Ave, Box 8115, St Louis, MO 63110.

mary reanastomosis of the RLN, presumably due to synkinesis. That this type of voice has not been reported in Crumley's series suggests that the more likely cause of immobility is the low number of axons in the ansa graft.

The hypoglossal nerve (nerve XII) is potentially a better donor nerve than the ansa cervicalis for laryngeal reinnervation, because it has many more axons and thus more "firepower." The RLN contains about 1,000 axons, of which about 25% are destined for the posterior cricoarytenoid (PCA) muscle and 75% for the adductor group.[10] The individual branches of the ansa have significantly fewer axons.[21] The human hypoglossal nerve averages 9,200 axons, divided into about 5 fascicles in the distal portion,[22] which should be more than enough to reanimate the arytenoid.

A more compelling reason to choose the hypoglossal nerve over the ansa cervicalis is that nerve XII has more appropriate physiologic activity; ie, it is active when vocal fold adduction is needed, during deglutition and during speech, and it is inactive during inspiration. Also, there is already significant clinical experience with using this donor nerve for facial reinnervation, and the morbidity has been low.[23] Surprisingly, there are no reports in the literature of using nerve XII for laryngeal reinnervation.

MATERIALS AND METHODS

Purpose-bred, conditioned, hound-type, female mongrel dogs, 6 to 12 months old, weighing 20 kg were used for these experiments. They were housed in a facility approved by the American Association for Accreditation of Laboratory Animal Care, and National Institutes of Health guidelines for animal care were followed strictly. The experimental protocol was approved by the animal care committee of the St Louis Veterans Affairs hospitals. Due to the high cost of long-term canine research, this preliminary study was limited to 5 animals.

Permanent Tracheostomy. This was performed according to our previously described method.[24] Briefly, the dogs were anesthetized with intravenous thiopental sodium. A low tracheotomy was made within tracheal rings 10 to 13, and general anesthesia was maintained with 1% to 2% halothane inhalant. The anterior half of the tracheal ring cartilage was removed, leaving laterally based mucosal flaps. An ellipse of skin was excised to reduce skin redundancy, and the stoma was matured with deep stay sutures between the trachea and dermis. The stoma was then allowed to heal for 2 weeks.

Assessment of Vocal Fold Motion. This was performed in each animal with an "infraglottic examination" (IGE). The dogs were placed on an examining table, fully awake, and a 4-mm rigid telescope (Karl Storz) connected to a video camera (Panasonic KS152) was directed through the tracheostomy, providing a view of the vocal folds from the infraglottic aspect (Fig 1A,B). Vocal fold activity could be observed spontaneously, or elicited by stimulating a swallow reflex by injecting 1 mL of water through one nostril. The dogs tolerated these examinations quite well. Laryngeal activity was recorded on a videocassette recorder (Mitsubishi BV2000) for later frame-by-frame analysis.

Intraglottic Adductory Force. Following IGE, the adductory force between the vocal folds was measured in the awake animal during spontaneous swallows. A 7.0-mm–inside diameter endotracheal tube was inserted into the subglottic space, and the balloon was inflated with 10 cm^3 of air.[25,26] The balloon pilot line was connected to a pressure transducer, and the baseline pressure was set at zero. A mark on the tube was made previously to indicate the position at which the midpoint of the balloon would be at the vocal fold level. The endotracheal tube was then pushed superiorly to the level of the mark, and this action generally stimulated a swallow reflex in the awake animal (Fig 1C). The pressure induced by vocal fold adduction squeezing on the balloon generated a waveform that was recorded on a chart recorder. It should be noted that these pressures give relative measures only, as the recorded pressure is dependent on the inflation pressure of the balloon (ie, they are uncalibrated). This method has been found to be reliable over time if the same inflation volume is used each time. Inflating with water rather than air did not significantly alter the results.

Nerve Transfer. General anesthesia was induced with intravenous thiopental and maintained with 1% to 2% halothane inhalant. A vertical midline incision was made, and the infrahyoid muscles were reflected laterally. The hypoglossal nerve was identified and dissected distally into the tongue. The right RLN was identified and dissected 2 cm inferior to the cricothyroid joint, where it was transected, and the distal (laryngeal) stump was redirected superiorly. The hypoglossal nerve was brought into approximation with the RLN, and end-to-end anastomosis was performed by a microsurgical neurorrhaphy technique with 4 to 6 epineural sutures. A 3- to 4-cm segment of the proximal (inferior) stump of the RLN was excised, and the free end was tied off.

The left side was used for controls. Two animals (Nos. 1 and 4) had the left RLN dissected and exposed as above, but it was allowed to remain intact

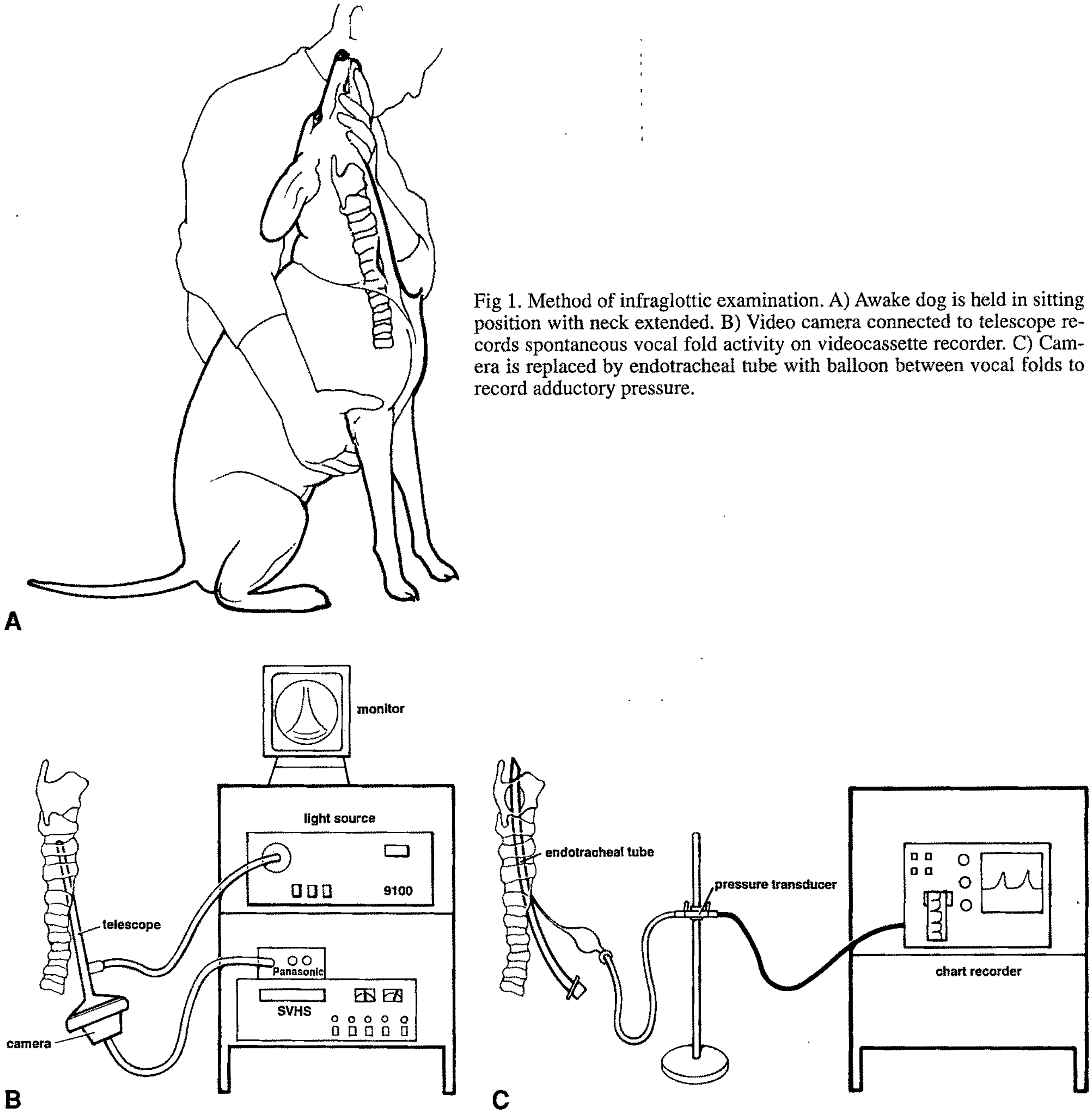


Fig 1. Method of infraglottic examination. A) Awake dog is held in sitting position with neck extended. B) Video camera connected to telescope records spontaneous vocal fold activity on videocassette recorder. C) Camera is replaced by endotracheal tube with balloon between vocal folds to record adductory pressure.

(normal group). Two animals (Nos. 2 and 3) had the left nerve transected and 4 cm excised, without repair (RLN section group); this excision was done at the time of the tracheostomy. The last animal (No. 5) had the left RLN divided as described above, but the neurorrhaphy was made to the sternohyoid branch of the ansa cervicalis.

Following the above procedures, the wounds were closed and allowed to heal. Special dressings or other wound care were not required.

Follow-up. Infraglottic examinations were performed monthly at postoperative months 2 through 6. Arytenoid motion was rated as absent, slight recovery (twitch noted but no medialization), partial recovery (incomplete medialization), complete recovery (vocal fold moves completely to midline), or normal (movement beyond midline was often seen). Intraglottic adductory pressures were measured during deglutition as described above, at the end of the sixth month.

RESULTS

All dogs had uncomplicated recoveries from the surgical procedures. There were no wound infections or tracheostomy problems. The diameter of the hypoglossal nerve was approximately 1.5 times that of the RLN in each case. The length of the hypoglossal nerve was more than adequate, and several centime-

TABLE 1. RESULTS OF HYPOGLOSSAL NERVE TRANSFER EXPERIMENTS

	Surgery		*Activity on Infraglottic Examination*				
Dog	*Side*	*Procedure*	*2 mo*	*3 mo*	*4 mo*	*5 mo*	*6 mo*
1	R	XII-RLN	NA	NA			
	L	Normal	Normal	Normal			
2	R	XII-RLN	NA	PR	CR	CR	CR
	L	RLN section	NA	NA	NA	NA	NA
3	R	XII-RLN	NA	NA	PR	CR	CR
	L	RLN section	NA	NA	NA	NA	NA
4	R	XII-RLN	NA	NA	PR	CR	CR
	L	Normal	Normal	Normal	Normal	Normal	Normal
5	R	XII-RLN	PR	CR	CR	CR	CR
	L	Ansa-RLN	NA	NA	SR	SR	SR

XII-RLN — hypoglossal–recurrent laryngeal nerve (RLN) anastomosis; ansa-RLN — ansa cervicalis–RLN anastomosis; NA — no activity; PR — partial recovery; CR — complete recovery; SR — slight recovery.

ters of each RLN were trimmed and discarded. In dog 5, the RLN was about 50% larger than the sternohyoid branch of the ansa cervicalis (the largest of the available branches).

At 3 months, dog 1 exhibited no spontaneous laryngeal motion on the nerve transfer side, and underwent neck exploration to determine whether the neurorrhaphy had become avulsed (eg, by vertical laryngeal motion or neck turning). Significant scar tissue was found around the hypoglossal nerve, and during the dissection the neurorrhaphy became separated. It was clear that this injury was caused by the exploratory procedure. In subsequent animals, it was found that return of activity sometimes occurred at greater than 3 months (see below); thus, it was felt this first dog had been explored prematurely. Because of this injury, this dog was considered a technical failure and was excluded from the remainder of the study.

All 4 remaining dogs showed partial spontaneous adduction at 2 to 4 months and full midline adduction at 3 to 5 months (Table 1). A sample of the IGE findings is given in Fig 2. The glottic closure observed by IGE on swallow was noted to be timed well with deglutition. Water injected to stimulate the swallow, and the absence of observed aspiration of this water suggests that the reinnervation afforded good protection against aspiration. Observation of the dogs' tongue activity during IGE demonstrated that tongue protrusion also caused adduction, although less than that seen on swallow. Between swallows, lesser tongue motion (eg, panting or licking) resulted in partial adduction only. Two of the dogs were also observed to occasionally produce loud barking, despite the presence of the tracheostomy.

It should be noted that 1 of the dogs with a paralyzed hemilarynx (No. 2) had enough adduction from the reinnervated side to completely close the glottic aperture. This was also seen with the dog that had the ansa transfer on the control side (No. 5). This latter dog also demonstrated different timing of the adductory activity between the two sides: the right side (hypoglossal-RLN) began to adduct earlier in the swallow than the left side (ansa-RLN, which only had a slight twitch of activity). This finding would be consistent with the normal sequence of activity of the respective donor muscles during a swallow.

The intraglottic adductory force measurements are given in Table 2. The values given are the mean of the 3 highest pressures recorded. Sample waveforms

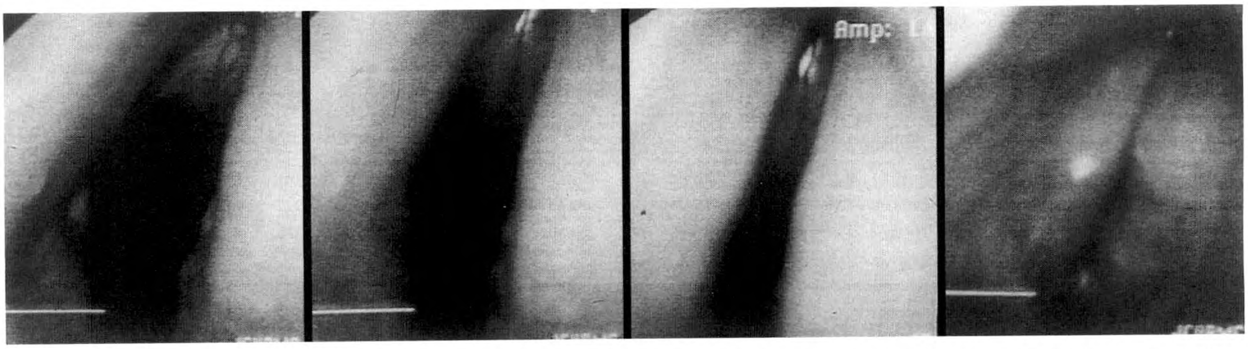


Fig 2. (Dog 4) Infraglottic examination. Photographs were taken of every other frame from videotape of spontaneous swallow. Time interval between frames is 0.04 second.

TABLE 2. INTRAGLOTTIC ADDUCTORY FORCE

	Intraglottic Adductory Force (mm Hg)
Dog 2	100.0
Dog 3	98.3
Dog 4	114.0
Dog 5	100.3
Reference values	
Normal	90-100
Unilateral vocal fold paralysis	60-70
Bilateral vocal fold paralysis	<30

are given in Fig 3. It should be noted that in some instances the pressures recorded were higher than the normal range. The normal values for intraglottic adductory pressure were obtained in prior experiments in our laboratory.

DISCUSSION

This study demonstrates that hypoglossal-to-RLN anastomosis is capable of restoring spontaneous adduction to a paralyzed hemilarynx. The strength of adduction appears to be at least as great as in the normal state, and possibly greater. Spontaneous adduction has usually not been reported with reinnervation using the ansa cervicalis, although adduction has been induced by electrical stimulation of the transferred ansa.[15,16] This finding highlights the fact that supramaximal stimulations do not exactly simulate the animal's natural activity. Supramaximal stimulation undoubtedly causes more depolarization than the animal would normally generate; also, the animal would not naturally maximally activate the adductors and abductors at the same time. The hypoglossal nerve provided enough firepower that adduction occurred in this study without the need for electrical stimulation.

The reinnervation of the common trunk of the RLN presumably allowed some axons to also reinnervate the PCA muscle. Some synkinesis is thus very likely, but because the adductor group was so well reinnervated and because it accounts for 75% of the RLN axons, it overpowered the PCA muscle, resulting in a net adduction.

It is interesting to note that these reinnervated vocal folds move back to the resting position after removal of the stimulus (via the hypoglossal graft, either on swallow or electrically). That the vocal folds did not drift to the paramedian position during the observation period suggests that some PCA reinnervation occurred to maintain a basal tone that balanced the adductor group. The rapid return from adduction to the resting position is probably not due to PCA activity, but rather, due to the myoelastic properties of the cricoarytenoid joint and ligaments.

This study demonstrates that dynamic adductory activity of the hemilarynx can be restored by hypoglossal-to-RLN neurorrhaphy. Although the number of dogs was small, the high success rate (100% of eligible dogs) is very encouraging. Several additional questions now need to be addressed.

1. What is the nature of the voice with this reinnervation method? If there is a significant amount of variable activity of the hypoglossal nerve, the voice could indeed be choppy or spasmodic-sounding, as Crumley[10] suggests. Unfortunately, this question cannot be answered in an animal model. Recent data from our laboratory suggest that in the normal state, the larynx adducts much more forcefully during swallowing than it does during speech (unpublished observations). The tongue, similarly, is more active during deglutition than during phonation. Potentially, this could mean that patients undergoing nerve XII–RLN reinnervation might obtain good tone with partial medialization during speech, and tight glottic closure during swallow, which would be the ideal result for rehabilitation of unilateral vocal fold paralysis. Human trials are needed to determine whether this result actually occurs in patients.

2. Is the voice and/or swallowing benefit of nerve XII–RLN transfer worth the sacrifice of another cranial nerve? The hypoglossal nerve has often been deemed a reasonable sacrifice in facial reanimation, where the benefit is usually facial tone with some mass movement. Morbidity from the denervated

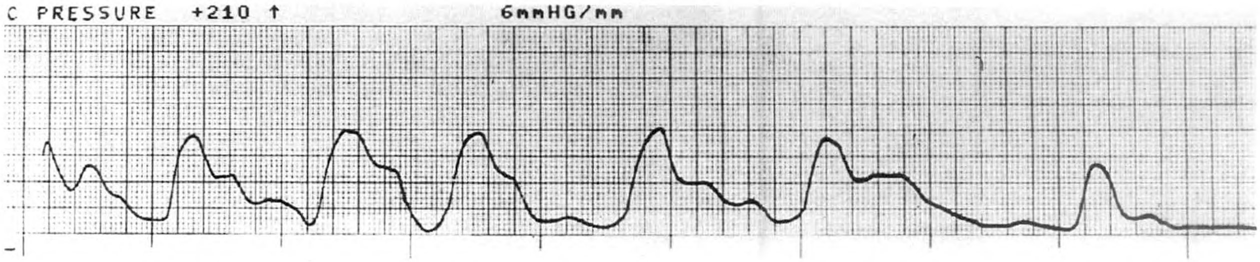


Fig 3. (Dog 5) Sample adductory force waveforms during series of spontaneous swallows. On y-axis, each small subdivision is 6 mm Hg.

hemitongue has been surprisingly low.[23] Would the combination of hypoglossal nerve and RLN paralysis on the same side be so morbid as to offset any appreciable benefit from this procedure? Perhaps a split hypoglossal nerve would provide enough reinnervation to gain active adduction but have even less donor site morbidity. This has been successfully employed in facial reanimation.[27,28]

3. What clinical settings would be appropriate for this type of reinnervation? If the RLN is injured too close to its entrance to the larynx, there would likely be inadequate length of the hypoglossal nerve in human subjects to perform primary nerve XII–RLN anastomosis (unlike in the dog model). This type of RLN injury might occur during thyroid surgery. If a nerve graft is used, regeneration must cross 2 anastomoses, with a likely further reduction in the number of regenerated axons. If the RLN is injured in the chest, as in cardiothoracic procedures, the laryngeal stump should have plenty of length to allow anastomosis to the hypoglossal nerve.

CONCLUSION

Hypoglossal-to-RLN anastomosis can successfully restore dynamic adductor function to a paralyzed hemilarynx, and appears to be superior to ansa cervicalis reinnervation in restoring active motion. Further research is needed to explore the potential benefits of this new procedure.

ACKNOWLEDGMENTS — The authors thank John Salmo and Dr Richard Doyle for their excellent support and care of our dogs.

REFERENCES

1. Isshiki N, Okamura H, Ishiwaka T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol (Stockh) 1975;80:465-73.

2. Isshiki N, Masahiro T, Sawada M. Arytenoid adduction for unilateral vocal cord paralysis: a comparison. Laryngoscope 1988;98:1200-4.

3. Crumley RL. Teflon versus thyroplasty versus nerve transfer: a comparison. Ann Otol Rhinol Laryngol 1990;99: 759-63.

4. Remacle M, Marbaix E, Hamoir M, Bertrand B, van den Eeckhaut J. Correction of glottic insufficiency by collagen injection. Ann Otol Rhinol Laryngol 1990;99:438-44.

5. Crumley RL. Unilateral recurrent laryngeal nerve paralysis. J Voice 1994;8:79-83.

6. Benninger MS, Crumley RL, Ford CN, et al. Evaluation and treatment of the unilateral paralyzed vocal fold. Otolaryngol Head Neck Surg 1994;111:497-508.

7. Sasaki CT, Leder SB, Petcu L, Friedman CD. Longitudinal voice quality changes following Isshiki thyroplasty type I: the Yale experience. Laryngoscope 1990;100:849-52.

8. Tucker HM, Rusnov M. Laryngeal reinnervation for cord paralysis: long-term results. Ann Otol Rhinol Laryngol 1981;90: 457-9.

9. Horsley JS. Suture of the recurrent laryngeal nerve with report of a case. Trans South Surg Gynecol Assoc 1909;22:161-7.

10. Crumley RL. Laryngeal synkinesis: its significance to the laryngologist. Ann Otol Rhinol Laryngol 1989;98:87-92.

11. Green DC, Berke GS, Graves MC, Natividad M. Physiologic motion after vocal cord reinnervation: a preliminary study. Laryngoscope 1992;102:14-22.

12. Fraser CH. The treatment of paralysis of the recurrent laryngeal nerve by nerve anastomosis. Ann Surg 1924;79:161-6.

13. Crumley RL. Update: ansa cervicalis to recurrent laryngeal nerve anastomosis for unilateral laryngeal paralysis. Laryngoscope 1991;101:384-8.

14. Crumley RL, Izdebski K. Voice quality following laryngeal reinnervation by ansa hypoglossi transfer. Laryngoscope 1986;96:611-6.

15. Green DC, Berke GS, Graves MC. A functional evaluation of ansa cervicalis nerve transfer for unilateral vocal cord paralysis: future directions for laryngeal reinnervation. Otolaryngol Head Neck Surg 1991;104:453-66.

16. Nasri S, Sercarz JA, Ye M, Kreiman J, Gerratt BR, Berke GS. Effects of arytenoid adduction on laryngeal function following ansa cervicalis nerve transfer for vocal fold paralysis in an in vivo canine model. Laryngoscope 1994;104:1187-93.

17. Tucker HM. Long-term results of nerve-muscle pedicle reinnervation for laryngeal paralysis. Ann Otol Rhinol Laryngol 1989;98:674-6.

18. May M, Beery Q. Muscle-nerve pedicle laryngeal reinnervation. Laryngoscope 1986;96:1196-200.

19. Tucker HM. Combined laryngeal framework medialization and reinnervation for unilateral vocal fold paralysis. Ann Otol Rhinol Laryngol 1990;99:778-81.

20. Nahm I, Shin T, Watanabe H, Maeyama T. Misdirected regeneration of injured recurrent laryngeal nerve in the cat. Am J Otolaryngol 1993;14:43-8.

21. Gottschall J, Neuhuber W, Muntener M, Mysicka A. The ansa cervicalis and the infrahyoid muscles of the rat. Anat Embryol (Berl) 1980;159:59-69.

22. Mackinnon SE, Dellon AL. Fascicular patterns of the hypoglossal nerve. J Reconstr Microsurg 1995;11:195-8.

23. Conley J, Baker DC. Hypoglossal-facial nerve anastomosis for reinnervation of the paralyzed face. Plast Reconstr Surg 1979;63:63-72.

24. Dahm JD, Paniello RC. Tracheostomy for chronic laryngeal experimentation. Otolaryngol Head Neck Surg 1998;118: 376-80.

25. Hvidegaard T, Vase P, Dalsgaard SC, Jorgensen K. Endolaryngeal devices for perioperative identification and functional testing of the recurrent nerve. Otolaryngol Head Neck Surg 1984;92:292-4.

26. Lipton RJ, McCaffrey TV, Litchy WJ. Intraoperative electrophysiologic monitoring of laryngeal muscle during thyroid surgery. Laryngoscope 1988;98:1292-6.

27. Cusimano MD, Sekhar L. Partial hypoglossal to facial nerve anastomosis for reinnervation of the paralyzed face in patients with lower cranial nerve palsies: technical note. Neurosurgery 1994;35:532-4.

28. Arai H, Sato K, Yanai A. Hemihypoglossal-facial nerve anastomosis in treating unilateral facial palsy after acoustic neurinoma resection. J Neurosurg 1995;82:51-6.

Ann Otol Rhinol Laryngol 108:1999

EXPRESSION PATTERN OF THE PLASMINOGEN ACTIVATOR–PLASMIN SYSTEM IN HUMAN CHOLESTEATOMA

MATTHIAS P. SCHÖNERMARK, MD
BIRTE K. ERBRICH, MD
PETER R. ISSING, MD
THOMAS LENARZ, MD
HANNOVER, GERMANY

The plasminogen activator–plasmin system plays a pivotal role in the delicately regulated process of extracellular matrix remodeling. Recent studies have shown that an imbalance of proteolytic enzymes over specific inhibitors in this system may lead to an aggressive, expanding, and infiltrating cellular phenotype. As cholesteatoma resembles a tumor in many ways, we investigated the pattern of expression for members of the plasminogen activator–plasmin system in 12 human cholesteatomas, using immunohistochemistry. As controls, 3 tympanic membranes and 4 ear canal skin specimens were used. In contrast to the tympanic membranes, all cholesteatoma specimens showed a strong expression of plasminogen at the basal epithelial cell layers. In ear canal skin, only the basal surface of the most basal epithelia stained discretely positive. The urokinase-type plasminogen activator (uPA) could be detected in the basal stratum of the cholesteatoma matrix and in the surrounding granulation tissue, while tissue-type plasminogen activator (tPA) was not detectable at all. Plasminogen activator inhibitor–1 (PAI-1) was expressed in both the granulation tissue and the granular cell layer of the matrix, but not in the basal epithelial cells; PAI-2 showed a pericellular expression pattern in the subbasal and granular cell layers. Neither uPA, tPA, nor the PAIs could be detected in tympanic membrane controls; ear canal skin showed the same staining pattern as cholesteatoma only for PAI-2. Our data demonstrate that there is a clear imbalance in favor of proteolytic activity in the basal epithelial layers of the cholesteatoma matrix, which might at least partly account for the aggressive behavior of this tumorlike lesion. Further, the pattern of expression resembles the pattern described for several epithelial malignancies.

KEY WORDS — basement membrane, cholesteatoma, extracellular matrix, middle ear, plasminogen, plasminogen activators.

INTRODUCTION

The crucial pathophysiologic event in cholesteatoma is the osteolytic destruction of the temporal bone, endangering important, otherwise protected structures, eg, the labyrinth, the facial nerve, and the carotid artery. In agreement with the early studies by Abramson and his group,[1,2] it is now well accepted that the degradation of the bony matrix is caused by proteolytic enzymes that are derived from the neighboring bone cells (osteoclasts and osteoblasts),[3,4] the granulation tissue (ie, the so-called "perimatrix"),[2] or the cholesteatoma epithelium itself.[5] Another pathologic phenomenon that requires active proteases and has been described recently is the disturbed ultrastructure of the cholesteatoma basement membrane.[6] This disturbance is the consequence of a derailed extracellular matrix (ECM) homeostasis that may account, at least partly, for the tumorlike behavior of the epithelium, and has been described for several carcinomas.[7]

Matrix metalloproteinases (MMPs) are a family of extracellular proteolytic enzymes that play a pivotal role in the physiological and pathologic turnover of ECM proteins. Their activity is tightly controlled by a sophisticated system of activators and inhibitors.[7,8] It has been shown recently that there is an imbalance in the expression of MMPs and their inhibitors in cholesteatoma that may cause an enhanced overall proteolytic activity.[5] This feature is also a typical property of many malignant tumors.[8]

The present study was designed to investigate the expression pattern of one of the most important physiologic activator systems for MMPs, the plasminogen activator–plasmin (PA/P) system in human cholesteatoma. Besides its MMP-activating ability,[9,10] the PA/P system itself is capable of degrading some ECM compounds.[11-14] Further, derailments in this system in favor of proteolytic activity have been correlated with degradation of bone[15,16]; a high level of invasiveness of tumors, leading to a poorer prognosis[17,18]; and "activation" of keratinocytes, as in inflammatory skin diseases or wound healing.[19-23] This underlines the potential relevance of the PA/P system in the pathophysiology of cholesteatoma.

MATERIAL AND METHODS

Cholesteatoma specimens were obtained from patients undergoing middle ear surgery for the first

---

From the Department of Otorhinolaryngology–Head and Neck Surgery, Hannover Medical School, Hannover, Germany. This work was supported by the Deutsche Forschungsgemeinschaft Scho633/2-1-065/97.

CORRESPONDENCE — Matthias P. Schönermark, MD, Dept of Otorhinolaryngology–Head and Neck Surgery, Hannover Medical School, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.

time. Twelve cholesteatomas (8 male, 4 female patients; mean age 34.0 years) were analyzed for the expression of members of the PA/P system, by immunohistochemical methods. As controls, tympanic membrane and normal ear canal skin were collected from patients undergoing total petrosectomy due to temporal bone malignancies (mean age 65.3 years). As a positive control for the anti–tissue-type plasminogen activator (tPA) antibody, cytospins of A2058 human melanoma cells were used.[24] To check for consistency of the expression pattern of the antigens, serial sections of all specimens were prepared and labeled with all antibodies. Further, different sections of the same cholesteatoma were produced to study variations in antigen expression in correlation to the morphology of the entire structure.

Preparation of Tissue Sections. Five-micron cryosections were cut in a Jung CM3000 cryostat (Leica, Bensheim, Germany) at –20°C, mounted on poly-L-lysine–coated slides, and prepared as follows: the sections were thawed, fixed with ice-cold acetone (10 minutes, room temperature), carefully washed with Tris-buffered saline (TBS), blocked with 10% normal swine serum in TBS, washed again, and incubated with the primary antibody. All specimens were examined histopathologically with routine hematoxylin and eosin staining.

Primary Antibodies. The primary antibodies were polyclonal anti-plasminogen (rabbit, Calbiochem, Bad Soden, Germany), at a dilution of 1:50 in TBS–bovine serum albumin; polyclonal anti–urokinase-type plasminogen activator (uPA); anti-tPA; anti–plasminogen activator inhibitor–1 (PAI-1); and anti–PAI-2 (goat, a generous gift from Dr Michael D. Kramer, Institute of Immunology, University of Heidelberg), diluted 1:50.[20-23,25]

Indirect Immunofluorescence. After incubation with the primary antibody for 1 hour at room temperature, sections were washed, and the second antibody was applied (donkey anti-rabbit; dichlortriacinyl-fluorescein–labeled, Dianova, Hamburg, Germany) for another hour in the dark. Sections were washed, air dried, and mounted with indirect immunofluorescence mounting medium (Immuno-Fluore, ICN, Eschwege, Germany). Preimmune sera and the omission of the primary antibody were used as negative controls. The slides were analyzed in a fluorescence microscope (Olympus BX60).

Avidin-Biotin Complex Method. For avidin-biotin complex (ABC) immunostaining, standard protocols were applied.[26] An immunolabeling kit was used (Coulter-Immunotech, Hamburg) that includes a biotinylated anti-goat antibody, ABC, and 3,3'-diaminobenzidine tetrahydrochloride as substratum. A specific positive signal displays as brown staining.

Alkaline Phosphatase–Anti–Alkaline Phosphatase Method. Standard protocols were used[26] that included a commercially available labeling and detection kit (Coulter-Immunotech). As substratum, fast red was used, which displays a bright red staining when activated by the enzyme.

RESULTS

Plasminogen. Fluorescence immunolabeling for plasminogen with a polyclonal antibody showed a strong positive staining of the basal 2 to 3 epithelial cell layers of all cholesteatoma specimens examined (Fig 1A). The stratum spinosum and the keratin layer were negative. Variant positive signals were seen in the granulation tissue of some specimens (8 of 12). In contrast, ear canal skin showed a discrete positive signal only on the basal surface of the stratum basale (Fig 1B). Subcutaneous tissue stained negative, and the keratin layer exhibited variant and patchy positivity. No signal could be detected in any of the tympanic membrane controls (data not shown).

Plasminogen Activators. The uPA immunolabeling with the ABC method revealed a positive signal in the basal epithelial stratum and in the granulation tissue (Fig 2A). This pattern was detected in 10 of 12 cholesteatoma specimens. The other 2 displayed variant and patchy signals with no clear correlation to morphologic structures, which may have been artifacts due to insufficient blocking or fixation. No staining could be found in any control specimen (Fig 2B, tympanic membrane; ear canal skin not shown). It should be noted that uPA was expressed in the same location as plasminogen. Neither cholesteatoma nor ear canal skin or tympanic membrane expressed tPA, as no positive alkaline phosphatase–anti–alkaline phosphatase signal could be detected (Fig 2C). However, cytospins with A2058 malignant melanoma tumor cells, which served as positive controls, revealed a strong positive signal (not shown).

Plasminogen Activator Inhibitors. The antibody for PAI-1 displayed strong staining of the granulation tissue and of the stratum corneum of all cholesteatoma specimens (Fig 3A), while the basal cell layers showed no positivity in the ABC reaction. The PAI-1 could not be detected in either the specimens from ear canal skin or in the tympanic membrane sections. In cholesteatoma, the PAI-2–specific staining was associated with the cell borders in the suprabasal epithelial stratum (Fig 3B), which corresponded to the positive signal found in the stratum granulosum of ear canal skin (data not shown). There was no staining in the basal cells or in the keratin, ie, the stratum corneum.

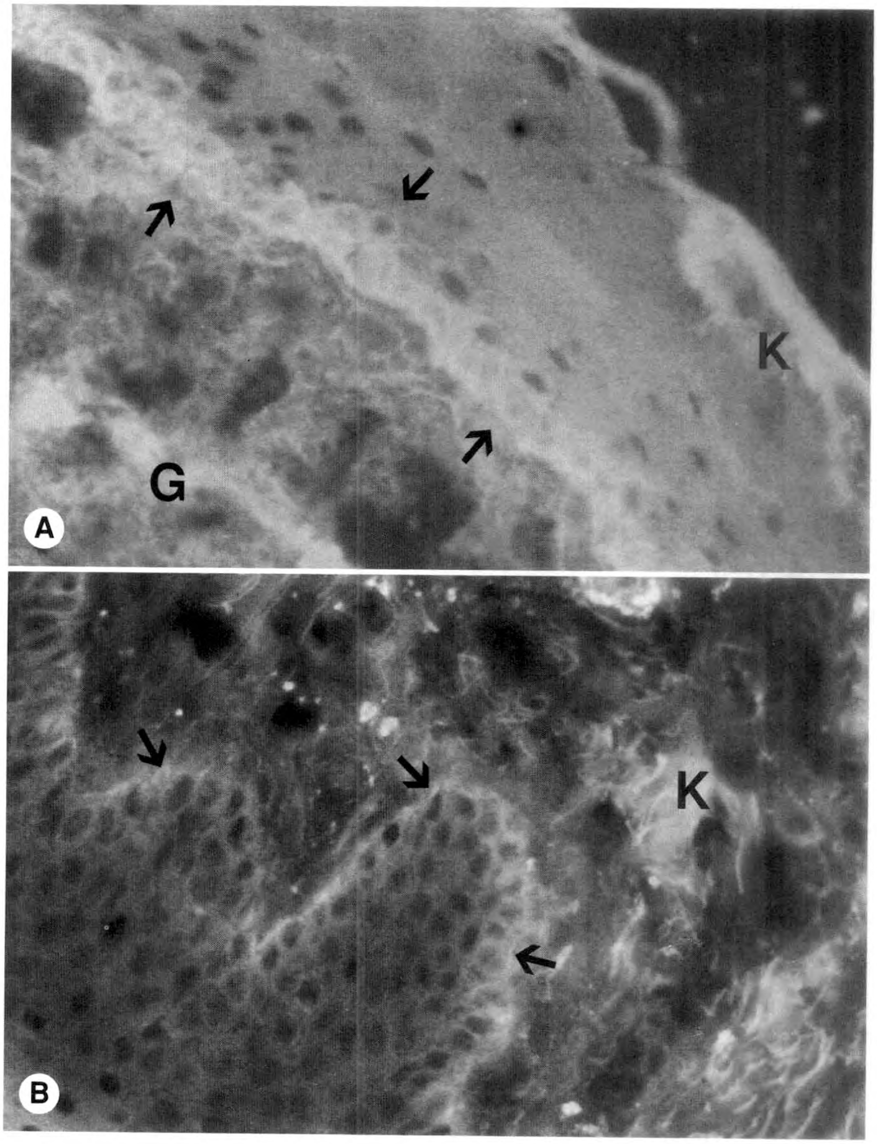


Fig 1. Expression of plasminogen on indirect immunofluorescence with polyclonal anti-plasminogen antibody (original ×400). K — keratin. A) In human cholesteatoma. Shows strong positive signal in basal 2 or 3 epithelial cell layers (arrows). G — granulation tissue. B) In human ear canal skin. Antibody detects plasminogen only at basal surface of most basal cells (arrows).

The immunohistologic results, ie, the expression of antigens of the PA/P system and their correlation to the morphologic structure of the cholesteatoma, are summarized in the Table.

Taken together, the examined cholesteatoma specimens displayed a strong plasminogen antigeneity in the basal epithelial stratum. This was colocalized with a positive signal for uPA. The PAIs could not be detected in the basal layers. Inhibitor expression was only revealed in the granulation tissue and in the suprabasal, ie, granular epithelial, stratum. While tympanic membranes were negative for all antigens tested, ear canal skin showed a discrete expression of plasminogen that was strongly confined to the basal surface of the stratum basale, and displayed a staining pattern for PAI-2 that was similar to that of cholesteatomas. No activator antigeneity or PAI-1 was detected.

The serial sections of the specimens revealed a remarkable consistency of the detected staining pattern. In only 2 of the 12 cholesteatomas could a colocalization of plasminogen and uPA *not* be detected. However, in 10 of 12 specimens, uPA and plasminogen, on the one hand, and PAI-1, on the other hand, were diametrically expressed. It should be noted that the expression pattern seemed to be most pronounced at the apex of the cholesteatoma "sac," while the base showed a somewhat weaker staining (not shown). However, the ratio and the localization of the antigens seemed to be consistent throughout the entire morphologic structure.

DISCUSSION

The integrity of the surrounding ECM and the underlying basement membrane is an important prerequisite for physiological cell growth and behavior. The ECM delivers important signals to the cells via integrins, and the balance of these signals de-

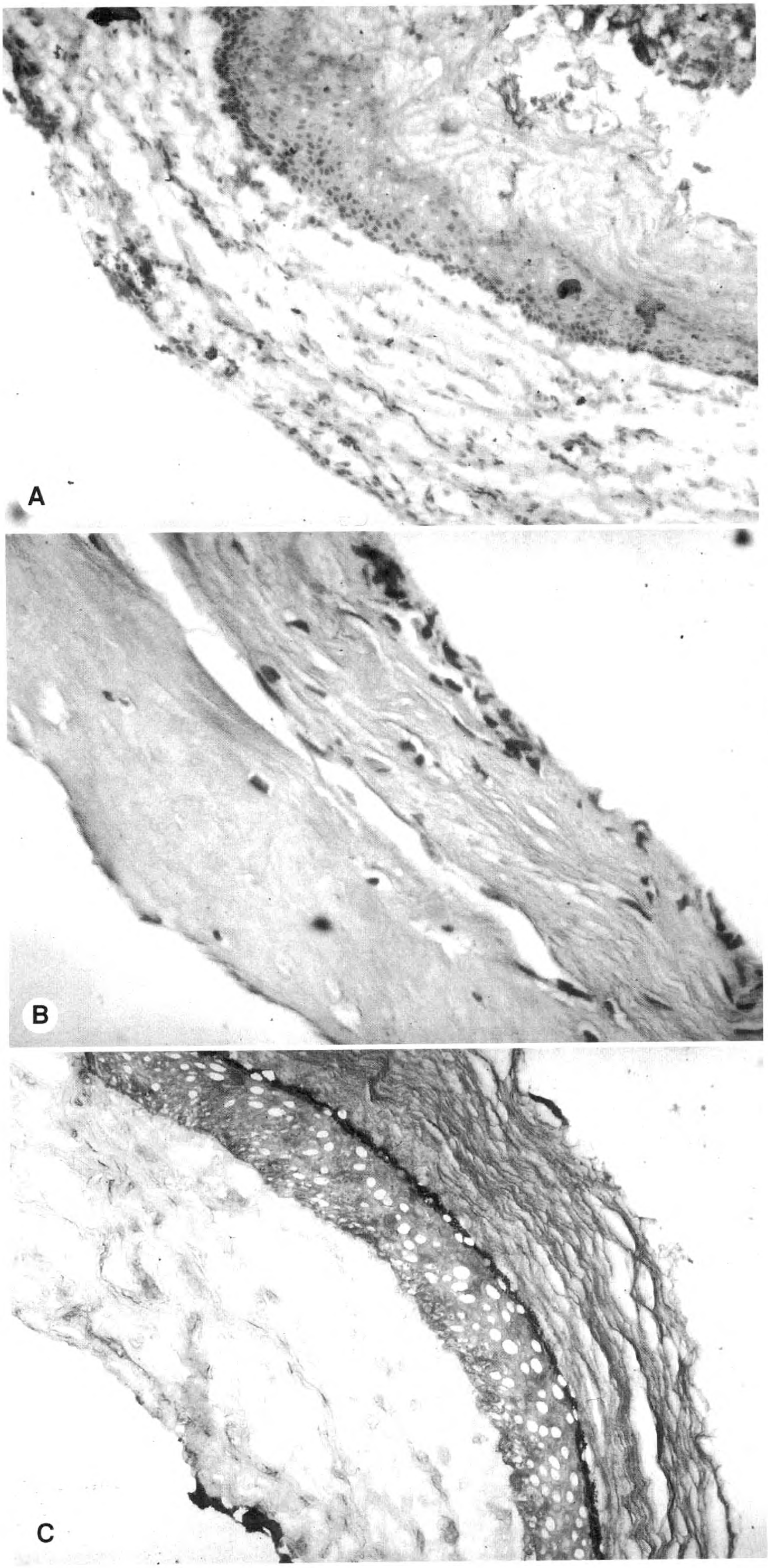


Fig 2. Expression of plasminogen activators. A) Urokinase-type plasminogen activator (uPA) in human cholesteatoma (avidin-biotin complex [ABC] method, original ×200). Brown positive signal is detected in basal epithelial cell layer and in granulation tissue. B) Tympanic membrane stained with anti-uPA (ABC method, original ×400). Negative staining indicates that uPA is not expressed. C) Expression of tissue-type plasminogen activator (tPA) in human cholesteatoma (alkaline phosphatase–anti–alkaline phosphatase [APAAP] method, original ×200). Cholesteatoma epithelium and granulation tissue show no detectable signal; tPA is not expressed.

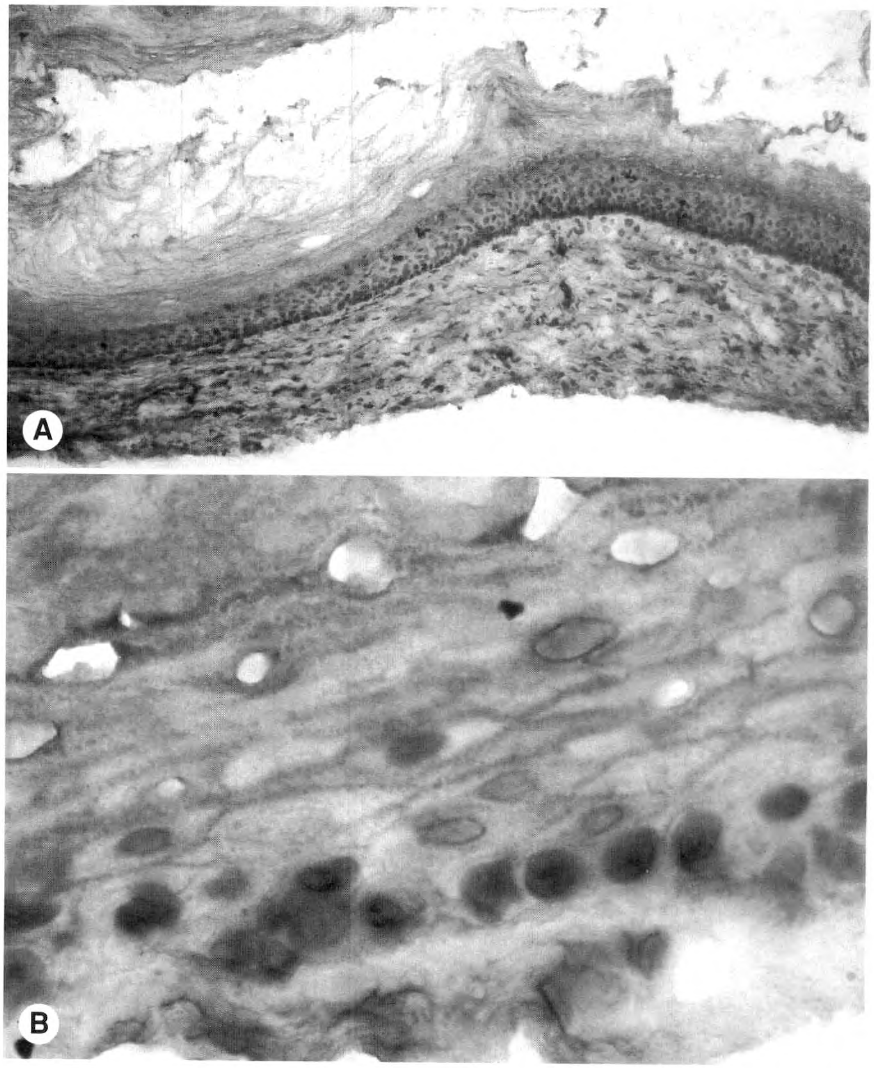


Fig 3. Expression patterns of plasminogen activator inhibitors (PAIs) in human cholesteatomas. A) PAI-1 expression (ABC method, original ×200). Brown staining indicates expression of PAI-1 in granulation tissue and in granular cell and keratin layers of cholesteatoma epithelium. Basal cells show no positivity. B) PAI-2 expression (APAAP method, original ×1,000). Pericellular signal can only be detected in suprabasal, ie, granular cell, layer of epithelium, while basal cells show no positivity.

fines the overall performance of the cell.[27] By a coordinate matrix turnover, ie, a physiologic equilibrium between matrix production and matrix degradation, the cells themselves influence their own behavior in an autocrine fashion. Thus, derailments of this homeostasis may lead to uncontrolled proliferation, and infiltrating and destructive growth of conglomerates of vitiated cells.[19,28] This pathophysiologic mechanism can be observed in malignant tumors, and we hypothesize that it is the underlying principle in cholesteatoma as well.

Our present results show that there is a clear imbalance between expression of the proteolytic members of the PA/P system and the inhibitors in the cholesteatoma epithelium. Of interest, different sections of the same cholesteatoma specimen revealed that the closer the epithelium is located to the cholesteatoma apex, the more pronounced this derailment seems to be. This suggests that the "external" inflammatory microenvironment could contribute at least partly to the imbalanced expression of the members of the PA/P system, eg, by inducing a differential tissue response.

Plasminogen, which can be detected in the basal epithelial layers, is mainly produced in the liver and transported via extracellular fluids to the periphery. There, it is "trapped" by capable cells that should bear plasminogen-binding regions on their surface.[21] These preferential binding sites, which may turn out to be receptors, have not been identified thus far. However, recent reports suggest that cytokeratin 8, a structural protein that is expressed in cholesteatoma epithelium,[29] as well as in some malignant epithelial tumors,[30] has potent plasminogen-binding capability.[31] The cell-bound plasminogen becomes activated by the specific plasminogen activators uPA and tPA,[21] which bind to specific cell surface receptors themselves, thereby potentiating their own activity.[11] While tPA plays a major role in the fibrinolytic arm of the PA/P system, uPA accounts for plasminogen activation in the tissue, thereby enabling plasmin to take part in active matrix remodeling.[14,18]

EXPRESSION PATTERN OF PLASMINOGEN ACTIVATOR–PLASMIN SYSTEM IN CHOLESTEATOMA AND IN CONTROL TISSUE

	Plasminogen	*uPA*	*tPA*	*PAI-1*	*PAI-2*
Cholesteatoma					
Granulation tissue	+/–	++*	–	++	–
Stratum basale	++	++*	–	–	–
Suprabasal layer	+	–	–	–	+/–
Stratum spinosum	–	–	–	–	+
Stratum corneum	–	–	–	+	–
Keratin	–	–	–	++	–
Ear canal skin	+†	–	–	–	+§
Tympanic membrane	–	–	–	–	–

uPA — urokinase-type plasminogen activator, tPA — tissue-type plasminogen activator, PAI — plasminogen activator inhibitor, ++ — strong expression, + — moderate expression, +/– — weak expression, – — no expression.

*Ten of 12 cholesteatomas.

†Stratum basale.

§Stratum granulosum.

Several studies have shown that malignant tumors overexpress uPA, which is colocalized with plasminogen in the tumor epithelium.[18,23] Further, uPA production seems to be an important prerequisite for epithelial migration.[19] The migration of epithelial cells on ECM, especially on vitronectin, is mediated by αvß5 integrins,[32] adhesion molecules that have been shown to be upregulated in cholesteatoma compared to normal skin.[33] Of interest, αvß5-mediated migration can be inhibited by blocking the interaction of uPA with its receptor.[32]

We detected uPA expression in the basal epithelial cell layers of 10 of 12 cholesteatomas, while there was no detectable expression in any of the control specimens. Moreover, the potent uPA inhibitor PAI-1 could only be detected in the perimatrix and only partly in the keratin layers of all of the studied cholesteatomas. There was no PAI-1 expression in any of the controls. The tPA could not be detected in any of the specimens, neither cholesteatomas nor controls. Of interest, levels of tPA are often decreased in human tumors, and this decrease has been correlated with tumor aggressiveness and clinical prognosis.[18] Only in melanoma cells is tPA upregulated; hence, we used a human melanoma cell line as a positive control for the antibody.[24] In epithelial tumors, PAI-2 is mainly found in the tumor stroma and is seen as a protective reaction against excessive proteolysis.[17] The PAI-2 was expressed only in the suprabasal and granular epithelial layers of the cholesteatoma specimens. This pattern was also seen in the ear canal skin controls; the tympanic membranes showed no PAI-2 positivity at all. Therefore, it can be assumed that the PAI-2 expression confines uPA activity to the very basal layers of the cholesteatoma epithelium and protects the cornified envelope from proteolytic damage. Recent studies suggest that besides its uPA-blocking activity, PAI-2 plays an important role in epithelial cell differentiation.[22] The pattern of PAI-2 expression that we observed in cholesteatoma resembles the motif that has been described in "activated" keratinocytes and epithelial tumors.[12,20,22]

Once activated by uPA, cell-bound plasminogen may unfold its multiple effects on ECM metabolism. Several matrix proteins, including fibronectin, are digestible by plasmin and uPA.[13] Fibronectin fragments, in turn, induce the expression and production of MMPs[34] and promote cell proliferation and migration, another typical and important motif of cholesteatoma.[35] The MMPs that can be detected in the cholesteatoma epithelium[5] are secreted in an inactive form and need extracellular activation. It has been shown that plasmin is one of the most potent physiologic MMP activators.[9,10] Further, uPA and plasmin can activate latent growth factors, eg, tumor growth factor β, basic fibroblast growth factor, and insulin-like growth factor.[15] It has been suggested that some of these factors play an important role in the pathophysiology of cholesteatoma.[36,37]

Thus, it may be hypothesized, on the basis of the present study, that the PA/P system plays an important role in the pathogenesis and promotion of middle ear cholesteatoma. The derailment of ECM homeostasis in cholesteatoma that has been described recently[5,6] may induce several autocrine feedback loops that result in hyperproliferative behavior and aggressive and destructive growth of the epithelial cells. The imbalanced PA/P system can easily potentiate this deleterious process by providing potent and uninhibited proteolytic enzymes.

CONCLUSIONS

Human middle ear cholesteatoma epithelium expresses proteins of the PA/P system. The expression pattern shows an imbalance in favor of the proteolytic arm of this system, with an overexpression of plasminogen and uPA, while PAI-1 cannot be detected. The PAI-2 that plays a major role in cellular differentiation processes is confined to the granular cell layer of the cholesteatoma epithelium. These motifs resemble malignant epithelial tumors, as does the previously described disturbance of ECM homeostasis. The derailment of normal cell-matrix interaction is caused by extracellular proteolytic enzymes, and the PA/P system plays a central role. As innovative tumor therapies target tissue degradation by proteolytic enzymes, further studies may reveal whether this therapeutic principle could be appropriate for the treatment of cholesteatoma concomitant with middle ear surgery.

ACKNOWLEDGMENTS — The authors thank Bettina Isernhagen for excellent technical assistance. We thank Dr M. D. Kramer for providing the polyclonal antibodies and for valuable discussion.

REFERENCES

1. Abramson M, Huang CC. Localization of collagenase in human middle ear cholesteatoma. Laryngoscope 1977;87:771-9.

2. Moriyama H, Honda Y, Huang CC, Abramson M. Bone resorption in cholesteatoma: epithelial-mesenchymal cell interaction and collagenase production. Laryngoscope 1987;97:854-9.

3. Uno Y, Saito R. Bone resorption in human cholesteatoma: morphological study with scanning electron microscopy. Ann Otol Rhinol Laryngol 1995;104:463-8.

4. Fuller K, Chambers TJ. Localisation of mRNA for collagenase in osteocytic, bone surface and chondrocytic cells but not osteoclasts. J Cell Sci 1995;108:2221-30.

5. Schönermark MP, Mester B, Kempf HG, Bläser J, Tschesche H, Lenarz T. Expression of matrix-metalloproteinases and their inhibitors in human cholesteatomas. Acta Otolaryngol (Stockh) 1996;116:451-6.

6. Sudhoff H, Bujía J, Borkowski G, et al. Basement membrane in middle ear cholesteatoma. Immunohistochemical and ultrastructural observations. Ann Otol Rhinol Laryngol 1996; 105:804-10.

7. Stetler-Stevenson WG, Liotta LA, Kleiner DE. Extracellular matrix 6: role of matrix metalloproteinases in tumor invasion and metastasis. FASEB J 1993;7:1434-41.

8. MacDougall JR, Matrisian LM. Contributions of tumor and stromal matrix metalloproteinases to tumor progression, invasion, and metastasis. Cancer Metastasis Rev 1995;14:351-62.

9. Murphy G, Atkinson S, Ward R, Gavrilovic J, Reynolds JJ. The role of plasminogen activators in the regulation of connective tissue metalloproteinases. Ann NY Acad Sci 1992;667: 1-12.

10. Nagase H. Activation mechanisms of matrix metalloproteinases. Biol Chem Hoppe Seyler 1997;378:151-60.

11. Cohen RL, Xi XP, Crowley CW, Lucas BK, Levinson AD, Shuman MA. Effects of urokinase receptor occupancy on plasmin generation and proteolysis of basement membrane by human tumor cells. Blood 1991;78:479-87.

12. Baker MS, Bleakley P, Woodrow GC, Doe WF. Inhibition of cancer cell urokinase plasminogen activator by its specific inhibitor PAI-2 and subsequent effects on extracellular matrix degradation. Cancer Res 1990;50:4676-84.

13. Marchina E, Barlati S. Degradation of human plasma and extracellular matrix fibronectin by tissue type plasminogen activator and urokinase. Int J Biochem Cell Biol 1996;28: 1141-50.

14. Mignatti P. Extracellular matrix remodelling by metalloproteinases and plasminogen activators. Kidney Int 1995;47 (suppl):S12-S14.

15. Allan EH, Martin TJ. The plasminogen activator inhibitor system in bone cell function. Clin Orthop Relat Res 1995; 313:54-63.

16. Koutsilieris M, Frenette G, Lazure C, Lehoux JG, Govindan MV, Polychronakos C. Urokinase-type plasminogen activator. A paracrine factor regulating the bioavailability of IGFs in PA-III cell–induced osteoblastic metastases. Anticancer Res 1993;13:481-6.

17. Pappott H, Gardsvoll H, Romer J, et al. Plasminogen activator inhibitor type 1 in cancer: therapeutic and prognostic implications. Biol Chem Hoppe Seyler 1995;376:259-67.

18. DeVries TJ, van Muijen GNP, Ruiter DJ. The plasminogen activation system in tumour invasion and metastasis. Pathol Res Pract 1996;192:718-33.

19. Morimoto K, Mishima H, Nishida T, Otori T. Role of urokinase type plasminogen activator (u-PA) in corneal epithelial migration. Thromb Haemost 1993;69:387-91.

20. Schaefer BM, Maier K, Eickhoff U, Bechtel M, Kramer MD. α_2-Antiplasmin and plasminogen activator inhibitors in healing human skin wounds. Arch Dermatol Res 1996;288:122-8.

21. Kramer MD, Schaefer B, Reinartz J. Plasminogen activation by human keratinocytes: molecular pathways and cell-biological consequences. Biol Chem Hoppe Seyler 1995;376:131-41.

22. Bechtel MJ, Schaefer BM, Kramer MD. Plasminogen inhibitor type-2 in the lesional epidermis of lupus erythematosus. Br J Dermatol 1996;134:411-9.

23. Inndorf S, Bechtel MJ, Reinartz J, Kramer MD. Cell density–dependent downregulation of urokinase-type plasminogen activator in normal but not in transformed human epidermal keratinocytes. Arch Dermatol Res 1996;288:783-5.

24. Rijken DC, Collen D. Purification and characterization of the plasminogen activator secreted by human melanoma cells in culture. J Biol Chem 1981;256:7035-41.

25. Rox JM, Reinartz J, Kramer MD. Interleukin-1ß upregulates tissue-type plasminogen activator in a keratinocyte cell line (HaCaT). Arch Dermatol Res 1996;288:554-8.

26. Robinson G, Ellis IO, MacLennan KA. Immunocytochemistry. In: Bancroft JD, Stevens A, eds. Theory and practice of histological techniques. Edinburgh, Scotland: Churchill Livingstone, 1990:413-36.

27. Hill CS, Treisman R. Transcriptional regulation by extracellular signals: mechanisms and specificity. Cell 1995;80:199-211.

28. Putnins EE, Firth JD, Uitto VJ. Keratinocyte growth factor stimulation of gelatinase (matrix metalloproteinase–9) and plasminogen activator in histiotypic epithelial cell culture. J Invest Dermatol 1995;104:989-94.

29. Lee RJ, Mackenzie IC, Hall BK, Gantz BJ. The nature of epithelium in acquired cholesteatoma. Clin Otolaryngol 1991;16:168-73.

30. Moll R, Franke WW, Schiller D, Geiger B, Krepler R. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 1982;31:11-24.

31. Hembrough TA, Li L, Gonias SL. Cell-surface cytokeratin 8 is the major plasminogen receptor on breast cancer cells and is required for the accelerated activation of cell-associated plasminogen by tissue-type plasminogen activator. J Biol Chem 1996;271:25684-91.

32. Yebra M, Parry GCN, Strömblad S, et al. Requirement for receptor-bound urokinase-type plasminogen activator for integrin αvß5–directed cell migration. J Biol Chem 1996;271: 29393-9.

33. Dallari S, Cavani A, Bergamini G, Girolomoni G. Integrin expression in middle ear cholesteatoma. Acta Otolaryngol (Stockh) 1994;114:188-92.

34. Bewsey KE, Wen C, Purple C, Homandberg GA. Fibronectin fragments induce the expression of stromelysin-1 mRNA and protein in bovine chondrocytes in monolayer culture. Biochim Biophys Acta 1996;1317:55-64.

35. Chao WY, Yuan QG, Huang CC. Localization of fibronectin in human middle ear cholesteatoma. Arch Otorhinolaryngol 1988;245:160-5.

36. Kojima H, Matsuhisa A, Shiwa M, et al. Expression of messenger RNA for keratinocyte growth factor in human cholesteatoma. Arch Otolaryngol Head Neck Surg 1996;122:157-60.

37. Marenda SA, Aufdemorte TB. Localization of cytokines in cholesteatoma tissue. Otolaryngol Head Neck Surg 1995;112:359-68.

≈

MIDDLE EAR MECHANICS

The Second International Symposium on Middle Ear Mechanics in Research and Otosurgery will be held October 21-24, 1999, in Boston, Massachusetts. For information, contact Harvard MED-CME, PO Box 825, Boston, MA 02117; telephone (617) 432-1525; web site http://www.med.harvard.edu/conted/.

≈

ADVANCED EAR SURGERY

A Compact Training Course in Advanced Ear Surgery (Endaural Tympano-meatoplasty and Enlarged Middle Fossa Approach) will be held May 16-19, 1999, in Erlangen-Nuremberg, Germany. For information, contact Prof Dr M. E. Wigand, Dept of ORL, University of Erlangen-Nuremberg, HNO Universitatsklinik, Waldstrasse 1, D-91054, Erlangen, Germany; telephone +49/9131/85-3141; fax +49/9131/85-6857.

Ann Otol Rhinol Laryngol 108:1999

RARE MIDDLE EAR ANOMALY IN A PATIENT WITH TURNER'S SYNDROME

ABDUL RAZAK RAHMAN HAMZAH, MBBS
MOHAMED AMIN JALALUDDIN, FRCS
RAJAGOPALAN RAMAN, MS
KUALA LUMPUR, MALAYSIA

A patient with Turner's syndrome presented with a rare anomaly of absent oval window, inferiorly placed facial nerve, and abnormal stapes. To our knowledge, this is the first report of this combination of malformations.

KEY WORDS — anomaly, facial nerve, middle ear, stapes.

INTRODUCTION

Isolated absence or atresia of the oval window and an abnormally placed or inferiorly placed facial nerve, with or without an abnormal stapes, associated with syndromes, have been reported before.[1-5] Various ear anomalies reported in association with Turner's syndrome are deformities of the pinna and external meatus,[6] bilateral perceptive hearing impairment,[7] frequent middle ear infections,[8] and stapes anomaly.[9] However, a combined association of aplasia or absence of the oval window, an inferiorly placed facial nerve, and a stapes anomaly in Turner's syndrome has not been described in the literature, to the best of our knowledge. We could not find one on an extensive literature search, and hence present this report.

CASE REPORT

A 27-year-old woman had received a diagnosis from the medical department of Turner's syndrome with the classic features of short stature and webbed neck. She presented to our department with a history of bilateral hearing loss since childhood. She could hear loud voices, and her speech development was reasonably good. She had been receiving thioridazine hydrochloride and trihexyphenidyl hydrochloride for

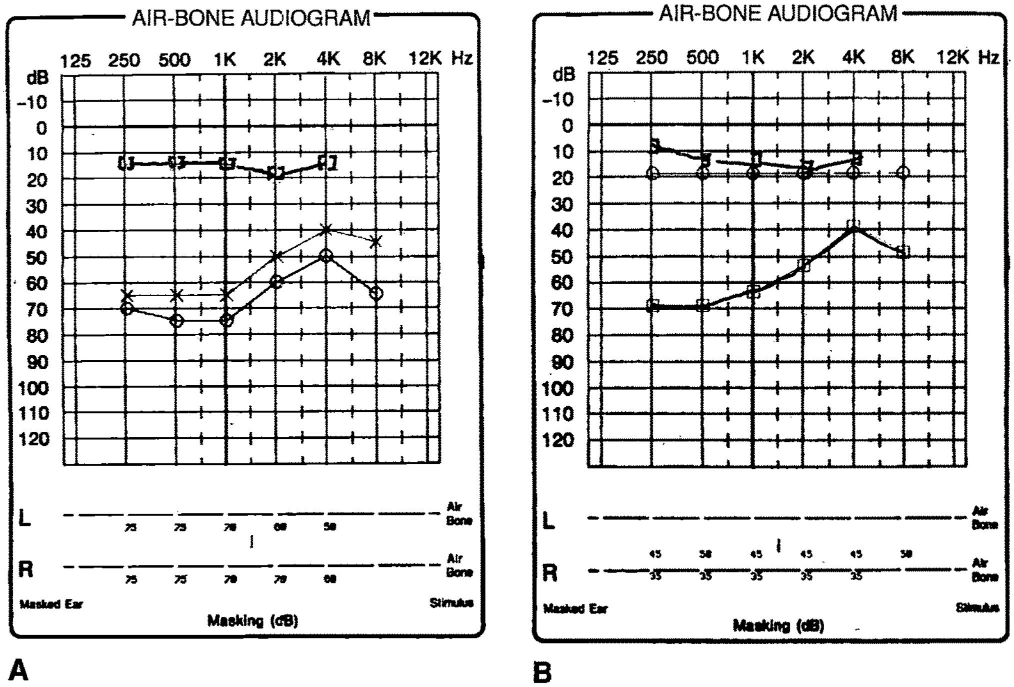


Fig 1. Audiograms. A) Preoperative, showing bilateral conductive hearing loss. B) Postoperative, showing almost normal hearing on right side.

From the Department of Otorhinolaryngology, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia.

CORRESPONDENCE — Rajagopalan Raman, MS, Dept of ENT, Faculty of Medicine, University Malaya, 50603, Kuala Lumpur, Malaysia.

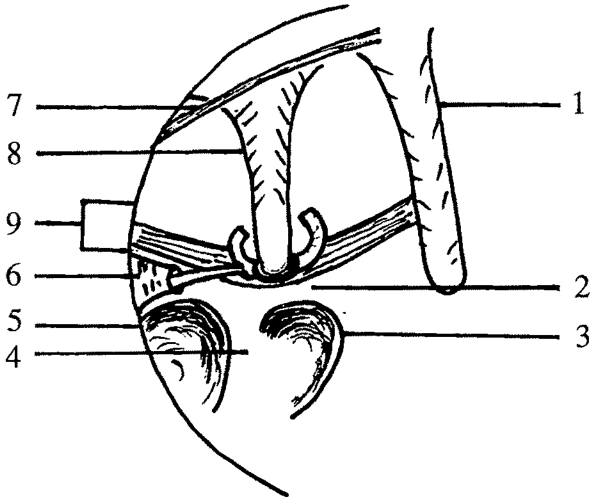


Fig 2. Right ear tympanotomy findings. 1 — Handle of malleus; 2 — promontory; 3 — round window niche; 4 — ponticulus; 5 — sinus tympani; 6 — pyramid with attached stapedius; 7 — chorda tympani; 8 — long process of incus; 9 — abnormalities including facial canal dehiscence, inferiorly placed facial nerve, absent oval window, and abnormal stapes with ill-developed stapedial crurae.

schizophrenia for the last 5 years. Findings of an otolaryngological examination were normal. Tuning fork tests revealed bilateral conductive hearing loss, which was confirmed with an audiogram (Fig 1A).

The patient underwent a right tympanotomy under general anesthesia. The middle ear revealed an intact stapes head attached to the lenticular process of the incus, a stapes neck with an attached stapedius tendon, ill-developed crurae of the stapes, dehiscence of the horizontal part of the facial canal, an inferiorly placed facial nerve sitting on the promontory, and an absent oval window (Fig 2). The lateral semicircular canal was not visible. The position of the oval window was assumed to be above the dehiscent facial nerve, which was sitting on the promontory. This was further estimated to be in line with the rudimentary stapes superstructure. The tympanotomy was done with a straight pick held parallel to the remnant of the superstructure and slid down so that the tip of the pick touched the medial wall of the middle ear. This was assumed to be the site of the oval window. The rudimentary stapes superstructure was then dislocated off the incus after cutting the stapedius tendon. A neo–oval window of 1 mm was created on the superior or cranial side of the facial nerve as assessed by the methods mentioned above. A 4.5-mm-long, 0.6-mm-diameter Teflon piston was interposed, with the loop of the piston on the long process of the incus above the lenticular process and the base of the prosthesis in the neo–oval window; this was similar to a stapedotomy done for otosclerosis. We found a description of a similar procedure by Sterkers and Sterkers.[10]

Postoperatively, the patient had severe vertigo, which completely recovered in a week. Postoperative follow-up after 3 months showed a remarkable subjective and objective improvement (Fig 1B).

COMMENT

It has been suggested that during normal development, the bony division between the inner ear and middle ear gradually becomes thinner, starting at the otic capsule at the level at which the stapes develops in the middle ear.[11] At the same time, the stapes takes a definitive form. It is probable that the developing stapes induces the thinning of the bony division that later becomes the footplate. In the same way, the otic capsule will influence the development of the stapes. Disruption of this complex mechanism may cause the types of anomalies we have described.[3] Total aplasia of the oval window is seen in association with severe deformity of the stapes in which the stapedial process hardly reaches the region of the oval window.[3] Our patient had this type of anomaly.

REFERENCES

1. Cremers CW, Teunissen E. Impact of syndromal diagnosis on surgery for congenital minor ear anomalies. Int J Pediatr Otorhinolaryngol 1991;22:59-74.

2. Lambert PR. Congenital absence of the oval window. Laryngoscope 1990;100:37-40.

3. Teunissen EB, Cremers CWRJ. Classification of congenital middle ear anomalies. Report on 144 ears. Ann Otol Rhinol Laryngol 1993;102:606-12.

4. Al Shihabi BM. Abnormalities of the facial nerve and middle ear. J Laryngol Otol 1984;98:391-3.

5. Sato R, Watanabe S, Fujita A, Fujimoto A, Inokuchi I, Ogura Y. Temporal bone pathology in congenital anomalies of the oval window and facial nerve. Auris Nasus Larynx 1985;12: 139-48.

6. Stratton H. Gonadal dysgenesis and the ears. J Laryngol Otol 1965;79:343-6.

7. Lindsten J, Tillinger K. Cytogenetical and clinical investigations in patients with Turner's syndrome. Endokrynol Pol 1965;16:141-9.

8. Szpunar J, Rybak M. Middle ear disease in Turner's syndrome. Arch Otolaryngol 1968;87:52-8.

9. Partsch C, Schmidt-Wittkamp E. Pterygium-Syndrom und Schwerhörigkeit. Arch Ohren Nasen Kehlkopfheilkd 1964; 183:336-8.

10. Sterkers JM, Sterkers O. Surgical management of the congenital absence of the oval window with malposition of the facial nerve. Adv Otorhinolaryngol 1988;40:33-7.

11. Anson BJ, Hanson JS, Richany SF. Early embryology of the auditory ossicles and associated structures in relation to certain anomalies observed clinically. Ann Otol Rhinol Laryngol 1960;69:428-47.

Ann Otol Rhinol Laryngol 108:1999

MURINE MODEL OF AUTOIMMUNE HEARING LOSS INDUCED BY MYELIN PROTEIN P0

HIROSHI MATSUOKA, MD
MEMPHIS, TENNESSEE

KUANG-CHUAN CHENG, PHD
MEMPHIS, TENNESSEE

MARC S. KRUG, PHD
MEMPHIS, TENNESSEE

YOSHIRO YAZAWA, MD
OTSU, JAPAN

TAI-JUNE YOO, MD, PHD
MEMPHIS, TENNESSEE

Myelin protein P0 has been identified as an autoantigen in inner ear diseases. In order to study autoimmune hearing loss, we performed brain stem auditory-evoked potential (BAEP) studies on P0-sensitized mice. Two P0-sensitized mice showed hunched posture, poor coat, loss of body weight, and abnormal walking with a waddling gait. About 25% of the P0-sensitized mice developed hearing loss. In the BAEP study, peak latencies of waves I, III, and V and the interpeak latency I-III were prolonged in the P0-sensitized hearing loss group of mice. Hearing thresholds were elevated in this group of mice in comparison with the control mice. Inflammatory cell infiltration was observed in the cochlear nerve region, and a reduced number of spiral ganglion cells was also detected. These results suggest that P0-sensitized mice are a useful model for studying autoimmune inflammation of the peripheral portion of the auditory system.

KEY WORDS — auditory-evoked potentials, autoimmune hearing loss, inner ear disease, myelin protein P0.

INTRODUCTION

There is extensive experimental and clinical evidence to support an autoimmune etiopathology for inner ear disease. Up to the present, a number of extracted proteins from bovine, guinea pig, and human inner ear have demonstrated reactivity with sera from patients with inner ear diseases.[1-3] We have reported that patients with Meniere's disease have antibodies against a 30 kd protein extracted from the inner ear of humans or guinea pigs.[1,4] Cao et al[5,6] have shown that patients with sensorineural hearing loss or Meniere's disease have antibodies against a 30 kd protein extracted from the inner ear of guinea pigs. They have identified this 30 kd protein as myelin protein P0 derived from the acoustic nerve and spiral ganglion.[7]

Myelin protein P0 is expressed in Schwann cells of the peripheral nervous system (PNS), but not expressed in the mammalian central nervous system (CNS).[8] Myelin protein P0 accounts for 50% to 60% of the peripheral myelin proteins and plays an important role in the compaction of myelin by means of homophilic interactions.[8-10] This protein is a cell adhesion molecule of the immunoglobulin supergene family.[11] Few interspecies amino acid variations were seen among the P0 sequences from several kinds of species.[12-14] Mutation of the P0 protein gene, located on chromosome 1q21-23, may lead to Charcot-Marie-Tooth disease type 1B.[15] Charcot-Marie-Tooth disease has been reported to be associated with hearing loss.[16,17] In these reports, many of the cases showed prolongation of interpeak latency (IPL) I-III in brain stem auditory-evoked potential (BAEP) studies, and this prolongation was supposed to be derived from peripheral nerves.[16,17] Although the incidence of abnormalities varied, similar abnormalities were reported in BAEP studies of patients with Guillain-Barré syndrome (GBS).[18,19]

In Lewis rats, an experimental autoimmune neuritis (EAN) has been induced by immunization of peripheral nerve myelin protein P0.[20] Diseased animals have many clinical and histopathologic findings that are parallel to those of GBS.[20] It is not clear whether these diseased animals suffer from hearing loss. This study was undertaken to investigate inflammation in the auditory nervous system induced

---

From the Department of Medicine, Division of Allergy and Immunology, University of Tennessee, Memphis, Memphis, Tennessee (Matsuoka, Cheng, Krug, Yoo), the Department of Otolaryngology, Shiga University of Medical Science, Otsu, Japan (Yazawa), and the Biomedical Research Center, Korea Advanced Institute of Science and Technology, Taejon, Republic of Korea (Yoo). This study was supported in part by the UTMG Allergy Supporting Fund and by National Institutes of Health grant DC00652-04A3. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Tennessee, Memphis.

CORRESPONDENCE — Tai-June Yoo, MD, PhD, Dept of Medicine, Division of Allergy and Immunology, University of Tennessee, Memphis, 956 Court Ave, Room H300, Memphis, TN 38163.

by myelin protein P0 immunization, which leads to hearing loss.

MATERIALS AND METHODS

Mice. DBA/1-lac (H-2^q) mice (6 to 10 weeks old) were purchased from Jackson Laboratory (Bar Harbor, Maine) and bred at the University of Tennessee, Memphis.

Purification of Myelin Protein P0. Fifty grams of bovine peripheral nerve was frozen in liquid nitrogen, ground and homogenized in 0.32 mol/L sucrose, and layered into a 0.85 mol/L sucrose solution. After centrifugation (25,000 rpm for 30 minutes), the interface was carefully removed, washed 3 times with deionized water, and lyophilized overnight. The protein was resuspended overnight in 30 mmol/L hydrochloric acid at room temperature. After centrifugation (5,000 rpm for 30 minutes), the supernatant that contained P2 protein was discarded. The precipitate that contained P0 protein was dissolved in chloroform:methanol (2:1) solution and neutralized by sodium hydroxide. The neutralized protein was dissolved in a 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) gel. The P0 protein at the 30 kd location was cut and eluted overnight from the gel by elution buffer (100 mmol/L sodium bicarbonate, 3% SDS, 8 mol/L urea, 25 mmol/L dithiothreitol). The eluted protein was separated from the gel by a 0.45 Millex GV syringe filter (Millipore Co, Bedford, Mass). Sodium dodecyl sulfate has been shown to inhibit the induction of immunity; therefore, we substituted deoxycholate for SDS in the purification process. Then, we added a mixture of phosphatidyl choline, and phosphatidyl ethanolamine plus cholesterol (50:45:5) and dialyzed the protein for 3 days in 10 mmol/L Tris buffer (pH 7.4) to replace the SDS. The purified P0 protein concentration was determined in a 10% SDS-PAGE gel.

SDS-PAGE. Electrophoresis was performed in a vertical electrophoresis apparatus (Life Technologies Inc) utilizing 10% SDS-PAGE. The acrylamide concentrations of the running gel and the stacking gel were 10% and 5%, respectively. After polymerization of the running gel, a 5% stacking gel was layered over the running gel. The polymerized gel was placed in the buffer-filled (250 mmol/L glycine, 25 mmol/L Tris, and 0.1% SDS; pH 8.3) electrophoresis apparatus. The samples were mixed with the same volume of gel-loading buffer (100 mmol/L Tris chloride pH 6.8, 4% SDS, 0.2% bromophenol blue, 20% glycerol, and 200 mmol/L dithiothreitol) and heated at 100°C for 3 minutes. Prestained high–molecular weight marker proteins (Life Technologies Inc) were used as molecular weight standards. The gel was run at 90 V for 7 hours. Separated proteins were then stained with Coomassie brilliant blue (Bio-Rad, Melville, NY) and destained with 45% methanol and 10% acetic acid in distilled water.

Immunization With P0 Protein. Purified P0 protein was mixed with an equal volume of complete Freund's adjuvant (CFA) containing killed *Mycobacterium tuberculosis* (1 mg/mL, Central Veterinary Laboratories, United Kingdom) for immunization. A group of 15 mice were immunized subcutaneously at the base of the tail (100 µg of P0 protein per mouse). The mice were also given an intraperitoneal dose of 300 ng of purified pertussis toxin (List Biological Laboratories Inc, Campbell, Calif) 24 and 72 hours after P0 protein immunization. Seven days later, the mice were boosted again with 50 µg of antigen in incomplete Freund's adjuvant. A group of 11 mice in the control group received CFA injections without P0 protein. These mice also received the same amount of pertussis challenge at 24 and 72 hours postinjection.

Recording of BAEPs. Under the anesthesia of ketamine hydrochloride (85 mg/kg) and xylazine hydrochloride (17 mg/kg), the BAEPs were recorded by a Nicolet CA-1000 system (Nicolet Biomedical Instruments, Madison, Wis). Investigation of the BAEPs was made with the mouse in a prone position in a dark, electrically shielded box. The body temperature was kept stable at approximately 37°C with a heating pad. Auditory stimuli were applied through an earphone (MDR-E515, Sony, Japan) that was placed 1 cm from the right (or left) ear canal. The response signals were recorded with subcutaneous needle electrodes. The active electrodes were placed in the vertex and in the right (or left) retrocochlear region and grounded on the back. The sound stimulus consisted of 100-microsecond clicks at a repetition rate of 11.4/s. The evoked auditory potentials were amplified $\times 10^4$, filtered with a bandpass between 150 and 1,500 Hz, and averaged from a total of 500 click-evoked responses for the first 10 milliseconds following stimulation. The stimulus intensity (decibels peak equivalent sound pressure level [pe SPL]) was calibrated with a sound level meter (model 800B, Larson Davis, North Provo, Utah). The hearing threshold was determined as the lowest intensity for a visible wave I. After immunization, the measurement of BAEPs was performed weekly for a period of 6 weeks. The peak latencies and interpeak latencies (IPLs) at a stimulation of 110 dB pe SPL and the hearing threshold were measured in each mouse.

Statistical Analysis. Statistical analyses were performed by the Mann-Whitney U test.

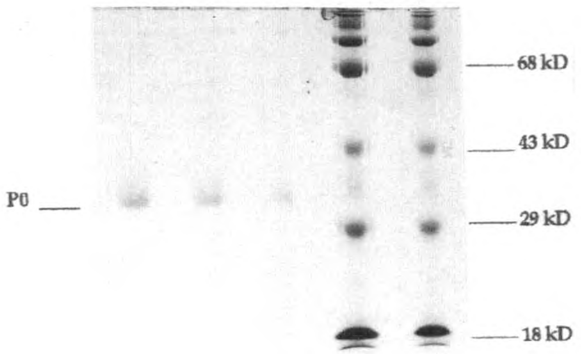


Fig 1. Estimation of purified P0 protein. On 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel, clear bands (3 lanes on left side) of purified P0 protein around 30 kd were detected. Two lanes on right side show molecular weights of protein standards.

Immunohistologic Studies. After deep anesthesia, the temporal bones of healthy Hartley strain female guinea pigs were fixed by transfusion via the heart with 10 mmol/L sodium periodate–75 mmol/L lysine–2% paraformaldehyde in 37.5 mmol/L sodium phosphate buffer (PLP; pH 6.4) solution and removed. The dissected tissues were fixed in PLP solution for 12 hours at 4°C. After fixation, inner ear samples were decalcified in Tris buffer (pH 7.2) containing 10% ethylenediaminetetraacetic acid at 4°C for 4 weeks. The tissues were incubated in 0.1 mol/L of phosphate buffered saline (PBS; pH 7.2) containing 20% sucrose for an additional 36 hours at 4°C and embedded in OCT compound (Miles Laboratories Inc, Elkhart, Ind). The frozen tissues were sectioned into 10- to 20-µm slices and rehydrated in PBS buffer (pH 7.2). The rehydrated sections were treated with 5% bovine serum albumin in PBS buffer (pH 7.2) to reduce the nonspecific reaction. The specimens were incubated with unlabeled mouse anti-P0 antibody (kindly provided by Dr J. P. Tomasi, Brussels, Belgium) as the primary antibody (1:1,000 dilution) for 4 to 7 days at 4°C. After they were rinsed with PBS buffer, the specimens were treated overnight with biotinylated anti-mouse IgG (1:200 dilution, Sigma Chemical Co, St Louis, Mo) at 4°C. After an additional rinse with PBS (pH 7.4), the specimens were incubated with avidin-biotin–horseradish peroxidase complex (Vectastain Elite ABC Kit, Vector Laboratories Inc, Burlingame, Calif) for 2 hours at room temperature and rinsed sufficiently with PBS. The color was developed with 0.02% 3,3'-diaminobenzidine (Sigma Co) in 0.05 mol/L of Tris–hydrochloric acid buffer (pH 7.6) with 0.01% hydrogen peroxide and 1% ammonium nickel (II) sulfate hexahydrate (Sigma Co). Finally, the specimens were rinsed with PBS to block the reaction. The specimens were dehydrated, cleared in xylene, and mounted for light microscopic examination. Phosphate buffered saline or nonimmune mouse serum (Pierce, Rockford, Ill), instead of primary antibody, was used as a control for the specificity of anti-P0 antibody. All the remaining procedures were the same as those described above.

Histopathologic Studies. A histopathologic study was performed on a few of the diseased mice that displayed clinical abnormalities. After painless sacrifice under deep anesthesia, the temporal bones from diseased mice were removed on days 14 and 17 postimmunization, and the tissues were fixed in 10% neutralized formaldehyde buffer solution for 2 days at 4°C. After fixation, they were decalcified in Tris buffer containing 10% ethylenediaminetetraacetic acid (pH 7.2) at 4°C for 1 week. The tissue was incubated in 0.1 mol/L of PBS (pH 7.2) containing 20% sucrose solution for an additional 36 hours at 4°C and embedded in OCT compound (Miles Laboratories Inc). The frozen sections were cut into 10-µm-thick slices and rehydrated in PBS buffer (pH 7.2).

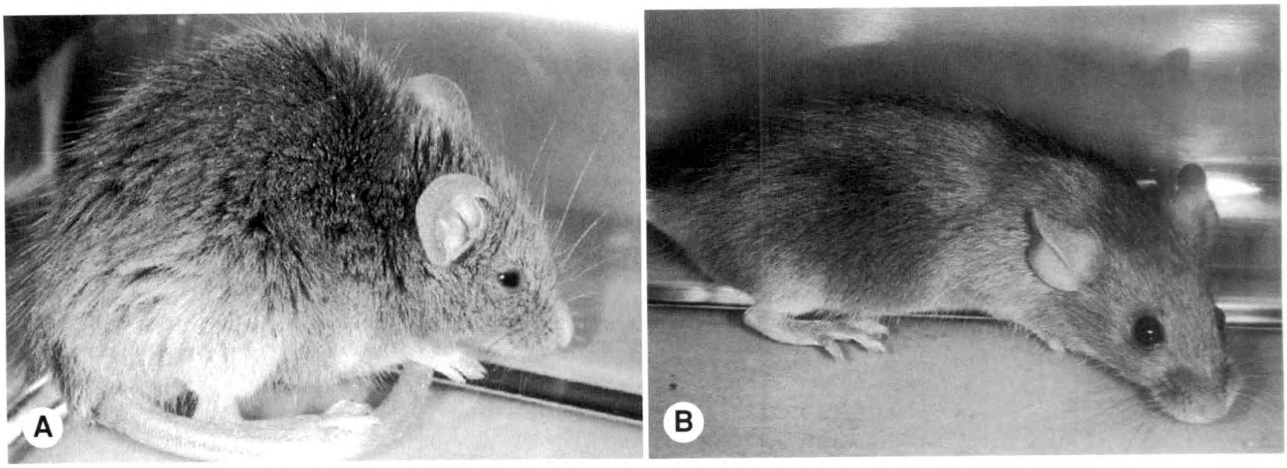


Fig 2. Clinical symptoms of P0-immunized mice. A) One of 2 (of total of 15) P0 protein–immunized mice that demonstrated hunched posture, poor coat, loss of body weight, and abnormal walking with waddling gait. B) No clinical symptoms were detected in complete Freund's adjuvant–injected control group of mice.

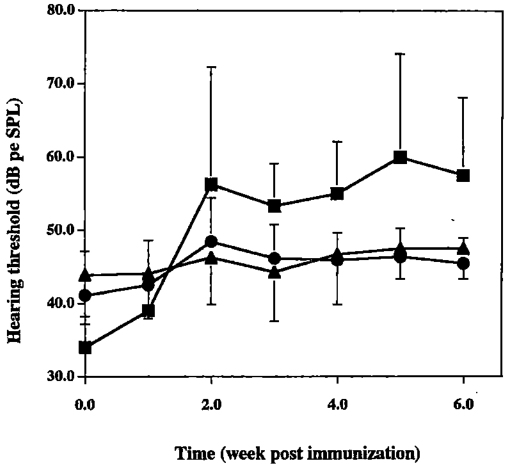


Fig 3. Changes in hearing threshold. In hearing loss group (squares), mean hearing threshold deteriorated 2 weeks after immunization, and hearing threshold shift continued until end of this study. No obvious change in hearing threshold was noted in complete Freund's adjuvant–injected mice (control; triangles) or non–hearing loss P0-immunized mice (circles) during observation period.

The rehydrated sections were stained with hematoxylin (Roboz Surgical Instrument Co, Washington, DC) and eosin (Harleco, Philadelphia, Pa). Then the sections were dehydrated, cleared in xylene, and mounted for light microscopic examination.

RESULTS

P0 Protein Purification. Due to the fact that P0 protein is an insoluble protein, SDS has sometimes been used to solubilize the P0 protein. However, SDS has been shown to inhibit the induction of immunity. Therefore, we used deoxycholate coupled with a mixture of phosphatidylcholine and phosphatidylethanolamine plus cholesterol (50:45:5) to substitute for SDS in the purification process. By using this method, we obtained a pure and soluble P0 protein that was suitable for immunizing mice for this hearing loss study (Fig 1).

Clinical Observations. Clinical symptoms were found in 2 of 15 P0 protein–sensitized mice. Those mice demonstrated hunched posture, poor coat, loss of body weight, and abnormal walking with a waddling gait (Fig 2). One of them demonstrated this condition on day 14 postimmunization and died on the same day. The other died on day 17 postimmunization. Other P0 protein–immunized mice seemed to be healthy, but they were predisposed to die easily under the anesthesia. No clinical symptoms were detected in the CFA-injected control group of mice.

Hearing Threshold Comparison in Control and P0-Immunized Mice. On day 14 postimmunization, 5 ears from 4 P0 protein–sensitized mice showed a hearing threshold shift of more than 20 dB. Other P0 protein–immunized mice did not show any significant changes in hearing threshold. Therefore, we divided P0 protein–immunized mice into 2 subgroups: a hearing loss group, which demonstrated an increased threshold of more than 20 dB, and a non–hearing loss group, which did not show significant changes (Fig 3). In the hearing loss group (P0 protein–sensitized mice), the mean hearing threshold deteriorated 2 weeks after immunization, and this hearing threshold shift continued till the end of the study. No significant changes in hearing threshold were noted in the CFA-injected and non–hearing loss P0-immunized mice during the observation period.

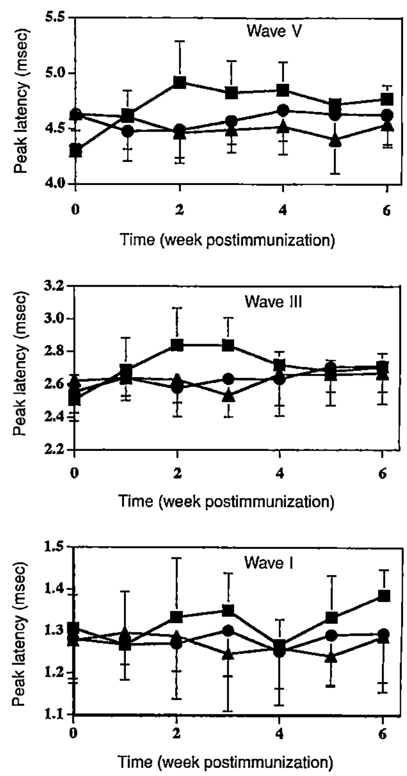


Fig 4. Changes in peak latency. Hearing loss group of mice demonstrated prolonged peak latencies of waves I, III, and V (squares). Prolongations in peak latencies of waves I and V started at 2 weeks postimmunization and lasted until end of study. Prolonged peak latency of wave III was noted in hearing loss group mice at 2 and 3 weeks postimmunization only and slowly decreased to normal peak latency. On other hand, control group of mice (triangles) did not show any prolongations in peak latencies of waves I, III, and V. In non–hearing loss group (circles), mean peak latency of wave V was inclined to be prolonged at 4 and 5 weeks postimmunization.

Comparison of Peak Latencies in Control and P0-Immunized Mice. As shown in Fig 4 and Table 1, only the represented peak latencies of waves I, III, and V were included. The hearing loss group of mice demonstrated prolonged peak latencies of waves I, III, and V. On the other hand, the control group of mice did not show any prolongations in the peak la-

TABLE 1. PEAK LATENCIES

Weeks After Immunization	*Group*	*Wave I*	*Wave III*	*Wave V*
0	Hearing loss	1.31 ± 0.08	2.51 ± 0.15	4.30 ± 0.18*†
	Non–hearing loss	1.28 ± 0.10	2.55 ± 0.18	4.63 ± 0.27
	Control	1.28 ± 0.11	2.62 ± 0.20	4.64 ± 0.36
1	Hearing loss	1.27 ± 0.13	2.69 ± 0.20	4.63 ± 0.22
	Non–hearing loss	1.27 ± 0.08	2.64 ± 0.11	4.48 ± 0.27
	Control	1.30 ± 0.08	2.64 ± 0.14	4.61 ± 0.29
2	Hearing loss	1.33 ± 0.14	2.84 ± 0.23†	4.92 ± 0.37*†
	Non–hearing loss	1.27 ± 0.13	2.58 ± 0.18	4.49 ± 0.25
	Control	1.29 ± 0.08	2.63 ± 0.14	4.46 ± 0.28
3	Hearing loss	1.35 ± 0.09	2.84 ± 0.17*†	4.83 ± 0.29
	Non–hearing loss	1.30 ± 0.11	2.63 ± 0.12	4.57 ± 0.21
	Control	1.25 ± 0.14	2.53 ± 0.13	4.49 ± 0.20
4	Hearing loss	1.27 ± 0.06	2.72 ± 0.08	4.85 ± 0.25
	Non–hearing loss	1.25 ± 0.13	2.63 ± 0.23	4.67 ± 0.28
	Control	1.26 ± 0.10	2.66 ± 0.19	4.52 ± 0.25
5	Hearing loss	1.33 ± 0.10	2.73 ± 0.02	4.72 ± 0.04
	Non–hearing loss	1.29 ± 0.12	2.71 ± 0.15	4.63 ± 0.29
	Control	1.24 ± 0.07	2.66 ± 0.19	4.41 ± 0.31
6	Hearing loss	1.39 ± 0.06	2.80 ± 0.04	4.77 ± 0.12
	Non–hearing loss	1.29 ± 0.12	2.71 ± 0.16	4.63 ± 0.29
	Control	1.29 ± 0.13	2.67 ± 0.19	4.54 ± 0.20

Data are in milliseconds (mean ± SD).
*$p < .05$ compared with control group.
†$p < .05$ compared with non–hearing loss group.

tencies of waves I, III, and V. In the non–hearing loss group, the mean peak latency of wave V tended to be prolonged at 4 and 5 weeks postimmunization. In the hearing loss group, the prolongations in the peak latencies of waves I and V started at 2 weeks postimmunization and lasted till the end of the study. The prolonged latency of peak III was noted in the hearing loss group mice at 2 to 4 weeks postimmunization only and slowly decreased to normal peak latency as observed in the control group of mice.

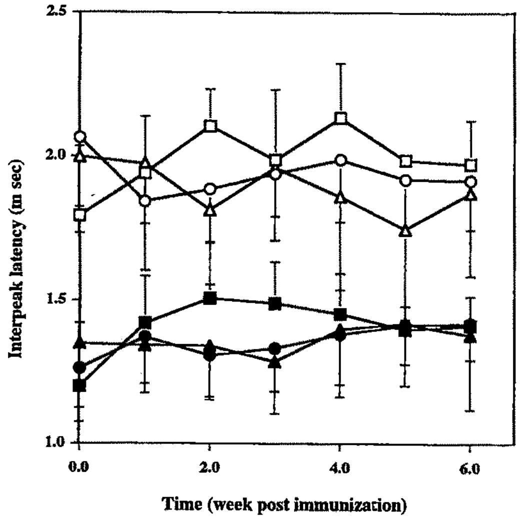


Fig 5. Changes in interpeak latency (IPL). In hearing loss group (dark squares), mean IPL I-III was prolonged at 2 and 3 weeks after immunization, then returned to normal as observed in control (dark triangles) and non–hearing loss (dark circles) groups of mice. No obvious prolongations were observed in mean IPL III-V in hearing loss (open squares), non–hearing loss (open circles), or control (open triangles) groups of mice.

Comparison of Interpeak Latencies in Control and P0-Immunized Mice. In the hearing loss group, the mean IPL I-III was prolonged at 1 week and persisted for 4 weeks postimmunization, then returned to normal as observed in the control group of mice (Fig 5 and Table 2). The mean IPL III-V was elevated, ranging from 1.75 to 2.00 milliseconds, in the control group of mice. Therefore, there is some difficulty in interpreting these results. A tendency for IPL III-V to be prolonged was detected at 2 and 4 weeks after immunization only in the hearing loss group (Fig 5 and Table 2).

P0 Protein Distribution in Cochlea of Guinea Pig. In the cochlear tissues from normal guinea pigs stained with anti-P0 antibody, positive staining reactions were detected along the cochlear nerve, and they were restricted within the myelinated areas of the cochlear nerve (Fig 6). The sections for negative control did not show any significant staining in the cochlear nerve.

TABLE 2. INTERPEAK LATENCIES

Weeks After Immunization	*Group*	*I-III*	*III-V*
0	Hearing loss	1.20 ± 0.22	1.79 ± 0.24†
	Non–hearing loss	1.26 ± 0.19	2.06 ± 0.24
	Control	1.35 ± 0.23	2.00 ± 0.26
1	Hearing loss	1.42 ± 0.16	1.94 ± 0.20
	Non–hearing loss	1.37 ± 0.16	1.84 ± 0.24
	Control	1.34 ± 0.17	1.97 ± 0.21
2	Hearing loss	1.51 ± 0.20†	2.10 ± 0.13*†
	Non–hearing loss	1.31 ± 0.15	1.89 ± 0.19
	Control	1.34 ± 0.18	1.81 ± 0.26
3	Hearing loss	1.49 ± 0.14	1.99 ± 0.24
	Non–hearing loss	1.33 ± 0.15	1.94 ± 0.15
	Control	1.29 ± 0.18	1.96 ± 0.25
4	Hearing loss	1.45 ± 0.14	2.13 ± 0.19
	Non–hearing loss	1.38 ± 0.18	1.99 ± 0.22
	Control	1.40 ± 0.24	1.86 ± 0.32
5	Hearing loss	1.40 ± 0.08	1.99 ± 0.02
	Non–hearing loss	1.41 ± 0.14	1.92 ± 0.18
	Control	1.42 ± 0.22	1.75 ± 0.31
6	Hearing loss	1.41 ± 0.10	1.97 ± 0.15
	Non–hearing loss	1.42 ± 0.13	1.92 ± 0.17
	Control	1.38 ± 0.26	1.87 ± 0.29

Data are in milliseconds (mean ± SD).
*p < .05 compared with control group.
†p < .05 compared with non–hearing loss group.

Detection of Cell Infiltration in Cochlear Nerve in P0-Immunized Mice. Mononuclear cell infiltration was observed in the cochlear nerve region, and a reduced number of spiral ganglion cells was also detected in the inner ear of the diseased mice that developed hearing loss (Fig 7). No significant structural changes were identified in the stria vascularis or middle ear regions of the same mice. These pathologic changes were not observed in the control group of mice (data not shown). It was difficult to interpret the changes in the organ of Corti from cryosection because of poor sample preservation. No histologic lesions were detected in the CNS area in the diseased mice.

DISCUSSION

In the present study, although the disease incidence in myelin protein P0–immunized mice is low, some interesting findings were noted. First, 4 of 15 myelin protein P0–immunized mice developed hearing loss characterized by an increased hearing threshold, and 2 of them demonstrated clinical symptoms. Waksman and Adams[21] reported that a large proportion of mice inoculated with peripheral nervous tissue did not show any symptoms at all. However, it was also described that some of the mice with PNS lesions were thin, bloated, irritable, or somewhat weak (hunched). They also presented a variety of peculiarities of posture and movement.[21] There is some argument about whether these symptoms are accurate expressions of peripheral neuropathy. Even so, it is still interesting that the clinical symptoms observed in the present study are similar to those described in the report of Waksman and Adams. Also, in Lewis rats immunized with P0 protein, the incidence of neurologic signs has been previously reported to be 30%,[20] nearly as low as the results in this study.

Second, many investigators have produced animal models of autoimmune inner ear diseases by using various antigens. To our knowledge, however, there is no report in the literature of an examination of hearing loss in P0 protein–immunized animals. Histopathologic findings showing lesions restricted to the cochlear nerve and spiral ganglion cells are characteristic of the present study. Animals immunized with antigens extracted from cochlear tissue have been reported to demonstrate various histologic changes. Terayama and Sasaki[22] described that the main histologic changes were found in the spiral ganglion, stria vascularis, and organ of Corti in guinea pigs immunized with homologous cochlea, and that endolymphatic hydropic changes were hardly seen. Harris[23] reported cochlear neuron loss, modiolar blood vessels with a perivascular mononuclear cell infiltrate, and the presence of extravasated red

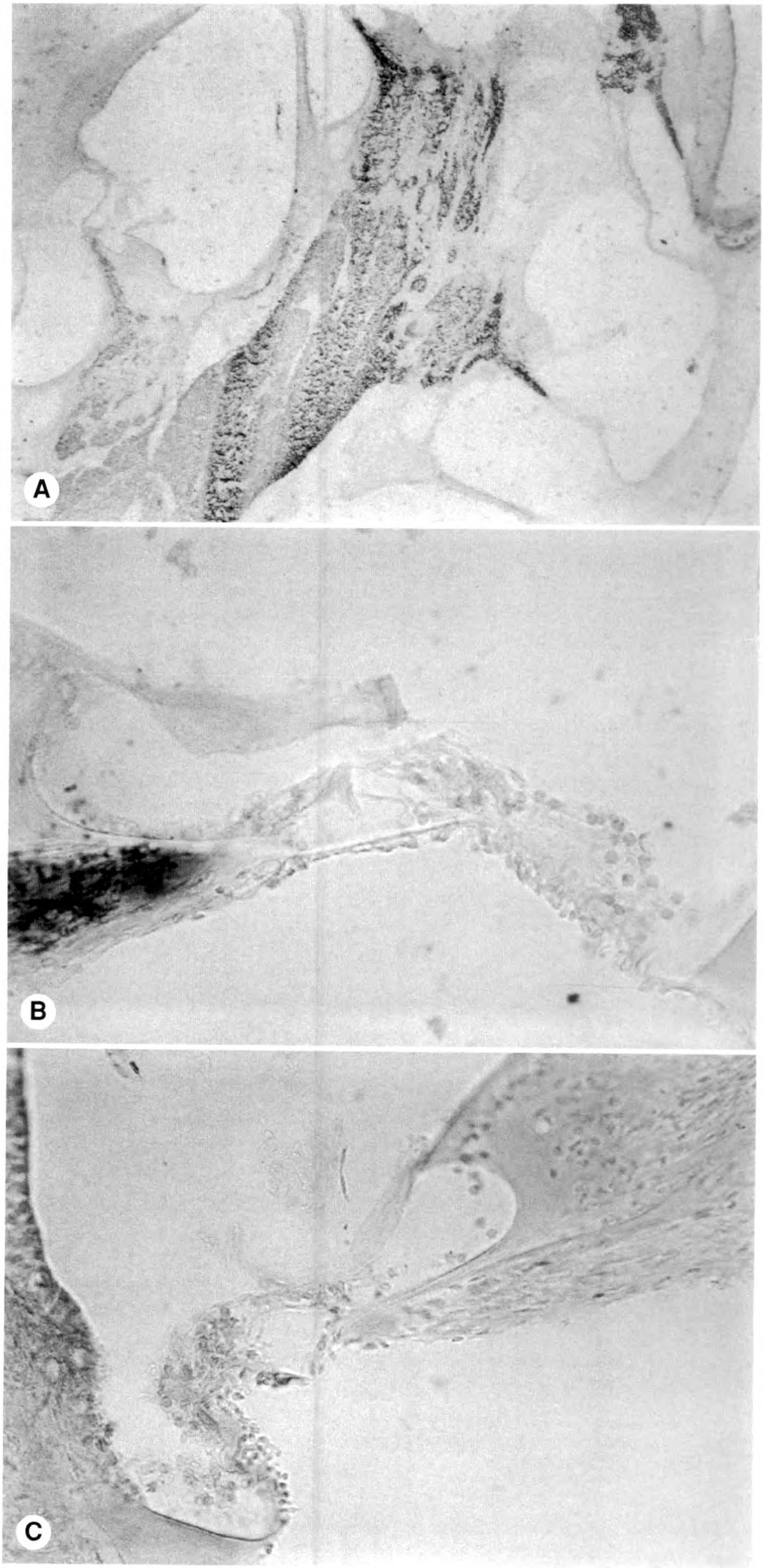


Fig 6. P0 protein distribution in normal guinea pig cochlea. In cochlea tissues from normal guinea pigs stained with anti-P0 antibody, positive staining reactions were A) detected along cochlear nerve (original ×10) and B) restricted within myelinated areas of cochlear nerve (original ×100). No staining was detected in any other part of guinea pig cochlea. C) Sections for negative control did not show any strong reactions in cochlear nerve (original ×50).

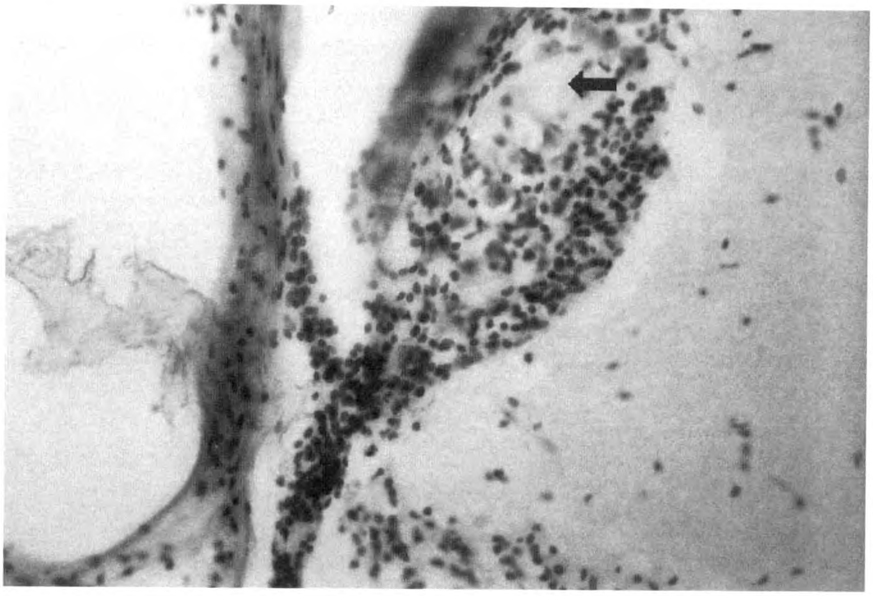


Fig 7. Cell infiltration in cochlear nerve in P0-immunized mice (original ×66). In sections of ear from diseased mice that developed hearing loss, mononuclear cell infiltration was observed in cochlear nerve region, and reduced number of spiral ganglion cells (arrow) was also detected.

blood cells in guinea pigs immunized with bovine inner ear tissue. He also mentioned that the organ of Corti and the stria vascularis appeared normal, and there were no signs of endolymphatic hydrops. Neither Harada et al[24] nor Soliman[25] observed any pathologic changes in the organ of Corti or the stria vascularis. Instead, endolymphatic hydrops was the main histologic change in their experiments. Protein P0 is a glycoprotein and is thought to be considerably different from the antigens from whole inner ear tissue even if P0 protein is included in the crude inner ear antigens. This may be the most likely explanation for the differences in the histologic findings between other studies and the present study.

Third, we were able to document the previously undescribed distribution of P0 protein in the guinea pig cochlea. Myelin protein P0 was present in the myelinated areas of the cochlear nerve fibers in the immunohistologic studies. In addition, mononuclear cell infiltration was detected in the cochlear nerve. It has been suggested that P0 protein plays an important role in generating the highly ordered structure of the myelin sheath and in the maintenance of compact myelin in the PNS.[12]

Further, there is evidence to suggest that P0 may be involved in the pathogenesis of demyelinating diseases of the PNS.[26] In the past, several investigators failed to produce demyelinating diseases with P0 protein,[27] but Milner et al[20] showed the ability of P0 to induce paralysis and histologic lesions resembling EAN. Up to the present, because of the solubility of myelin protein P2, it has been used most commonly to induce peripheral nerve lesions.[28] Myelin protein P2 is soluble in aqueous solution, while myelin protein P0 is not. Passive transfer of myelin protein P2–specific T cells and anti-myelin antibody induces EAN.[29] These results suggest that EAN is a disease involved in both the cellular and humoral immune systems.[29] A dominant expression of the T cell receptor (TCR) Vβ8 subfamily (TcrbV8) has been identified in the EAN rat (P2 epitope peptide–immunized rat). Comparison of these myelin protein P2–specific TcrbV8 sequences with the myelin basic protein (MBP)–specific TcrbV8 sequences indicates that myelin protein P2–specific TCR is less restricted and does not overlap with MBP-specific TCR.[30] Higher expression of interferon-γ has been observed before the onset of the disease, followed by the expression of tumor growth factor β and interleukin-4 in the lymph nodes and spleen tissue at the remission stage of the disease.[31] Second, by utilizing a panel of synthetic P0 peptides, 2 distinct T cell epitopes within the sequences 56-71 and 180-199 have been identified that can induce T cell–mediated EAN in the Lewis rat.[11] Third, the early T cell responses to P0 protein may be important in the pathogenesis, in some cases, of GBS.[32] Fourth, homologies between P0 and Epstein-Barr virus, cytomegalovirus, and varicella zoster virus proteins have been detected, as these pathogens have all been clearly associated with GBS.[33] Fifth, it has been shown that serum from patients with monoclonal IgM gammopathy and polyneuropathy had reactivity with P0 protein.[34] Although it is still unknown whether the attack of the immune system on the virus could result in injuries to myelin protein P0 and leads to autoimmune ear disease with sensorineural hearing loss, these findings not only indicate an involvement of P0 protein in EAN, but also lend support to the association of prodromal infections with GBS.

Finally, prolongation of both the peak latencies of waves I, III, and V and IPL I-III was detected in the hearing loss group. In patients with GBS or hereditary motor-sensory neuropathy who showed abnormal BAEPs, the greater part of the abnormalities was a prolonged IPL I-III.[16-19] This is in agreement with our results. These findings, including our results, strongly support the hypothesis that the appearance of hearing loss in the current study was due to dysfunction of peripheral nerve conductance. Statistically significant differences in the BAEP data were detected more frequently between the hearing loss group and the control group than between the hearing loss group and the non–hearing loss group. Two clinical cases that had abnormal prolongation of IPL I-III with a normal hearing threshold have also been reported.[16] This case report and our data suggest that some mice in the non–hearing loss group had a tendency to develop the disease asymptomatically.

Here, however, we should discuss why the increased hearing threshold persisted while prolonged peak latencies of waves I, III, and V and a prolonged IPL I-III returned to normal at 2 to 3 weeks postimmunization. Return to normal by prolonged peak latencies and IPLs is thought to be a direct reflection of the recovering state of the damaged cochlear nerve. On the other hand, it is very important that the hearing threshold determined in this experiment and the actual threshold of the action potentials in the cochlear nerve are quite different from each other. It is tempting to speculate that the amplitude of wave I was reduced because of poor synchronization of the responses of respective cochlear nerve cells in the recovering state. Onishi and Manabe[35] indicated that there is the possibility of a difference between subjective and objective hearing thresholds when the subject has a problem with synchronization. This may be why the changes in the amplitude of wave I did not parallel those in the peak latencies.

The incidence of disease in animals immunized with P0 protein seems to be dependent on various factors, such as the species of the animals, the method by which the antigen was prepared, and the method of immunization. Therefore, we need further studies to clarify this point.

Although the identity of the 30 kd band was not confirmed by anti-P0 monoclonal antibody reactivity, sufficient evidence exists to establish that the vast majority of the protein in this band is indeed P0. The steps in the purification protocol up to the SDS-PAGE step were minor variations on previously published P0 purification protocols.[8-10] These steps separate the membrane-bound proteins from soluble proteins and then remove most of the acid-soluble proteins such as P2 from the remaining membrane-bound proteins. The resulting SDS-PAGE profiles are essentially identical to those in previously published gels in which P0 was purified and identified. Since P0 has been shown to be the major component of the myelin fraction (50% to 60%), and the band pattern of all proteins matched previous results, it is reasonable to presume that the isolated 30 kd protein band was P0. The virtual insolubility of the isolated fraction in the absence of detergent is also consistent with this protein's being membrane protein P0. A very slight contamination with other membrane-bound 30 kd proteins cannot be entirely excluded, but the strong immunologic response was most likely due to P0.

In summary, we have purified myelin protein P0 and shown that this purified protein can induce hearing loss in mice. This inflammation resembles the natural process of inflammation in the PNS. Our results presented here suggest that the audiologic changes of myelin protein P0–immunized mice were comparable to those in GBS or Charcot-Marie-Tooth disease, and that immunologic reactions identified in the spiral ganglion and cochlear nerve were responsible for the audiologic abnormalities.

ACKNOWLEDGMENTS — The authors thank Drs Thomas Shen, James Clark, and Mikio Suzuki for technical support of the experiments, Lewis Pointer for animal care, and Jeff Parker for critical review of the manuscript. Dr Matsuoka is grateful to Dr K. Kitajima, Professor and Chairman of the Department of Otolaryngology, Shiga University of Medical Science, Japan, for giving him the opportunity to study abroad in Professor Yoo's laboratory.

REFERENCES

1. Joliat T, Seyer J, Bernstein J, et al. Antibodies against a 30 kilodalton cochlear protein and type II and IX collagens in the serum of patients with inner ear diseases. Ann Otol Rhinol Laryngol 1992;101:1000-6.

2. Yamanobe S, Harris JP. Inner ear–specific autoantibodies. Laryngoscope 1993;103:319-25.

3. Kosaka K, Yamanobe S, Tomiyama S-I, Yagi T. Inner ear autoantibodies in patients with sensorineural hearing loss. Acta Otolaryngol Suppl (Stockh) 1995(suppl 519):176-7.

4. Suzuki M, Krug MS, Cheng K-C, Yazawa Y, Bernstein J, Yoo T-J. Antibodies against inner-ear proteins in the sera of patients with inner-ear diseases. ORL 1997;59:10-7.

5. Cao M-Y, Gersdorff M, Deggouj N, Warny M, Tomasi J-P. Detection of inner ear disease autoantibodies by immunoblotting. Mol Cell Biochem 1994;146:157-63.

6. Cao MY, Deggouj N, Gersdorff M, Tomasi J-P. Guinea pig inner ear antigens: extraction and application to the study of human autoimmune inner ear disease. Laryngoscope 1996; 106:207-12.

7. Cao MY, Dupriez VJ, Rider MH, et al. Myelin protein P0 as a potential autoantigen in autoimmune inner ear disease. FASEB J 1996;10:1635-40.

8. Greenfield S, Brostoff S, Eylar EH, Morell P. Protein composition of myelin of the peripheral nervous system. J Neurochem 1973;20:1207-16.

9. Ishaque A, Roomi MW, Szymanska I, Kowalski S, Eylar EH. The P0 glycoprotein of peripheral nerve myelin. Can J Biochem 1980;58:913-21.

10. Filbin MT, Walsh FS, Trapp BD, Pizzey JA, Tennekoon GI. Role of myelin P0 protein as a homophilic adhesion molecule. Nature 1990;344:871-2.

11. Linington C, Lassmann H, Ozawa K, Kosin S, Mongan L. Cell adhesion molecules of the immunoglobulin supergene family as tissue-specific autoantigens: induction of experimental allergic neuritis (EAN) by P0 protein–specific T cell lines. Eur J Immunol 1992;22:1813-7.

12. Lemke G, Axel R. Isolation and sequence of a cDNA encoding the major structural protein of peripheral myelin. Cell 1985;40:501-8.

13. Sakamoto Y, Kitamura K, Yoshimura K, Nishijima T, Uyemura K. Complete amino acid sequence of P0 protein in bovine peripheral nerve myelin. J Biol Chem 1987;262:4208-14.

14. Hayasaka K, Nanao K, Tahara M, et al. Isolation and sequence determination of cDNA encoding the major structural protein of human peripheral myelin. Biochem Biophys Res Commun 1991;180:515-8.

15. Kulkens T, Bolhuis PA, Wolterman RA, et al. Deletion of the serine 34 codon from the major peripheral myelin protein P0 gene in Charcot-Marie-Tooth disease type 1B. Nat Genet 1993;5:35-9.

16. Satya-Murti S, Cacace AT, Hanson PA. Abnormal auditory evoked potentials in hereditary motor-sensory neuropathy. Ann Neurol 1979;5:445-8.

17. Raglan E, Prasher DK, Trinder E, Rudge P. Auditory function in hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease). Acta Otolaryngol (Stockh) 1987;103:50-5.

18. Schiff JA, Cracco RQ, Cracco JB. Brainstem auditory evoked potentials in Guillain-Barré syndrome. Neurology 1985;35:771-3.

19. Nelson KR, Gilmore RL, Massey A. Acoustic nerve conduction abnormalities in Guillain-Barré syndrome. Neurology 1988;38:1263-6.

20. Milner P, Lovelidge CA, Taylor WA, Hughes RAC. P0 myelin protein produces experimental allergic neuritis in Lewis rats. J Neurol Sci 1987;79:275-85.

21. Waksman BH, Adams RD. A comparative study of experimental allergic neuritis in the rabbit, guinea pig and mouse. J Neuropathol Exp Neurol 1956;15:293-332.

22. Terayama Y, Sasaki Y. Studies on experimental allergic (isoimmune) labyrinthitis in guinea pigs. Acta Otolaryngol (Stockh) 1963;58:49-64.

23. Harris JP. Experimental autoimmune sensorineural hearing loss. Laryngoscope 1987;97:63-76.

24. Harada T, Matsunaga T, Hong K, Inoue K. Endolymphatic hydrops and III type allergic reaction. Acta Otolaryngol (Stockh) 1984;97:450-9.

25. Soliman AM. Experimental autoimmune inner ear disease. Laryngoscope 1989;99:188-93.

26. Archelos JJ, Roggenbuck K, Schneider-Schaulies J, Linington C, Toyka KV, Hartung H-P. Production and characterization of monoclonal antibodies to the extracellular domain of P0. J Neurosci Res 1993;35:46-53.

27. Uyemura K, Suzuki M, Kitamura K. Studies on myelin proteins in human peripheral nerve. Adv Exp Med Biol 1978;100:95-115.

28. Whitaker JN. The protein antigens of peripheral nerve myelin. Ann Neurol 1981;9(suppl):56-64.

29. Spies JM, Pollard JD, Bonner JG, Westland KW, McLeod JG. Synergy between antibody and P2-reactive T cells in experimental allergic neuritis. J Neuroimmunol 1995;57:77-84.

30. Zhang X-M, Esch TR, Clark L, et al. Neuritogenic Lewis rat T cells use Tcrb chains that induce a new Tcrb-V8 family member. Immunogenetics 1994;40:266-70.

31. Gregorian SK, Clark L, Heber-Katz E, Amento EP, Rostami A. Induction of peripheral tolerance with peptide-specific anergy in experimental autoimmune neuritis. Cell Immunol 1993;150:298-310.

32. Khalili-Shirazi A, Hughes RAC, Brostoff SW, Linington C, Gregson N. T cell responses to myelin proteins in Guillain-Barré syndrome. J Neurol Sci 1992;111:200-3.

33. Adelmann M, Linington C. Molecular mimicry and the autoimmune response to the peripheral nerve myelin P0 glycoprotein. Neurochem Res 1992;17:887-91.

34. Bollensen E, Steck AJ, Schachner M. Reactivity with the peripheral myelin glycoprotein P0 in serum from patients with monoclonal IgM gammopathy and polyneuropathy. Neurology 1988;38:1266-70.

35. Onishi S, Manabe T. A guide to objective audiometry using averaging techniques. Kyoto, Japan: Kimpodo, 1976:76-94.

Ann Otol Rhinol Laryngol 108:1999

THREE-DIMENSIONAL QUANTIFICATION OF "STILL" POINTS DURING NORMAL FACIAL MOVEMENT

SUSAN E. COULSON, MAPPSC
GLEN R. CROXSON, MBBS FRACS
WENDY L. GILLEARD, MSC
SYDNEY, AUSTRALIA

This study investigated the 3-dimensional displacement of points on the face that were thought to be still during facial movement. These points are currently used to measure displacement of moving facial regions during assessment of normal facial movement and treatment interventions following facial nerve paralysis. It is, however, unknown if these places are "still" points. The Expert Vision Motion Analysis System was used to collect and analyze data on 42 normal subjects during facial movement. No point on the face was found to be still during facial expression. However, several points were present with very small movements for each individual expression. These were termed "reference" points. These small movements may be the result of system noise, physiological tremor, skin movement, or head-holder movement during facial expressions. Future studies of the displacement of the markers during facial movement in both normal subjects and patients with facial nerve paralysis may take into account the contribution of the "reference" point displacements to the overall facial movement.

KEY WORDS — facial expression, facial nerve, facial paralysis, movement, reference values.

INTRODUCTION

To understand more about dysfunctional facial movement such as that following facial nerve paralysis, we must better understand the parameters of normal facial movement. To date, some studies of facial movement have assumed that parts of the face do not move during facial expression.[1,2] Certain facial points such as the tragus, the nasal apex, and a midpoint on the nose have also been proposed to move very little, and have been nominated as "facial reference points."[1-4] However, no evidence was provided that these points did not move, or had relatively small movement during facial expression. As these points have been used to measure the excursion of moving facial marker points, the validity of movement data collected on this basis is questionable.

One pilot study of 3 men and 3 women has used an objective, 3-dimensional (3-D) computerized method to investigate the 3-D displacement of facial reference points for a protocol of 6 facial expressions.[5] It was found that there was no completely still point on the face during facial expression; however, there were reference points with very small movements for each individual expression. As the pilot study used low subject numbers, it may not be statistically relevant in a larger population. Therefore, this current study aimed to investigate increased subject numbers to determine facial reference points during normal facial movement.

METHOD

Forty-two subjects, 21 men and 21 women, with no past history of facial nerve paralysis formed the study group. The age range was 19 to 44 years, with the mean age being 32.33 years. The subjects were volunteers, and the study was approved by The University of Sydney Ethics Committee. All testing was performed by the first author at the Biomechanics Laboratory, School of Exercise and Sports Science, The University of Sydney.

Seven specific facial points that were previously thought not to move during facial expression were chosen following a review of the literature.[1,2,6-9] These points included 1) midpoint at the uppermost part of the forehead, 7 cm vertically above the soft tissue nasion (7 cm mid-forehead point); 2) soft tissue nasion; 3) midnasal point, 1.5 cm vertically below the soft tissue nasion; 4) subnasale; 5) left midtragus; 6) right mid-tragus; and 7) 3 cm vertically below the mid–lower vermilion border. The subjects had 7 spherical retroreflective markers, approximately 7 mm in size, attached on the proposed facial reference points with Scotch Double Stick Tape (3M). The subjects then performed a series of facial movements. The protocol of facial expressions (at rest, forehead raise, eye closure, nose wrinkle, maximum smile, pout, lips pulled down) was thought to reflect

---

From the School of Exercise and Sports Science, The University of Sydney (Coulson, Gilleard), and the Department of Otorhinolaryngology, Royal Prince Alfred Hospital (Croxson), Sydney, Australia. Supported by a grant in aid from the Garnett Passe and Rodney Williams Memorial Foundation.

CORRESPONDENCE — Susan E. Coulson, MAppSc, Suite 5, 35 Fourth Ave, Eastwood, NSW 2122, Australia.

TABLE 1. MEAN DISPLACEMENT AND STANDARD DEVIATION OF REFERENCE POINTS FOR FACIAL MOVEMENTS

Movement	*Facial Reference Point*	*Horizontal Axis (mm)*	*Vertical Axis (mm)*	*Anterior-Posterior Axis (mm)*	*3-D Combined (mm)*
Forehead raise	3InfML lip	0.61 ± 0.44	0.26 ± 1.28	0.73 ± 0.49	0.99
Eyes closed	3InfML lip	1.00 ± 0.77	2.11 ± 2.09	1.09 ± 0.93	2.58
Nose wrinkle	Left tragus	1.07 ± 0.62	1.43 ± 0.95	1.66 ± 0.94	2.44
Maximum smile	Nasion	1.46 ± 0.93	1.34 ± 0.97	1.83 ± 1.74	2.27
Pout	Nasion	1.44 ± 1.04	1.58 ± 1.56	2.06 ± 2.27	2.60
Lips pulled down	Nasion	1.53 ± 0.78	1.71 ± 1.00	1.79 ± 1.55	2.48
Mean		1.19	1.41	1.53	2.40

3InfML lip — 3 cm inferior to mid–lower lip; nasion — soft tissue nasion.

movement in the branches of the facial nerve and had been used in previous studies.[5,10] The subjects were asked to perform each movement maximally 3 times in succession over an 8-second period, relaxing after each attempt.

Four NEC TI23A video cameras with an electronic shutter speed of 0.001 s and a filming frequency of 60 Hz were used to record the marker positions. Cameras were placed in the recommended "umbrella configuration,"[11] with 2 cameras at 30° and 2 at 70° on either side of the subject's face, at a distance of 1.2 m. Four 75-W spotlights were mounted on the camera tripods in line with the optical axis of the cameras. The Expert Vision Motion Analysis System (Motion Analysis Corporation, Santa Rosa, Calif) was integrated with the video cameras to collect data and allow computerized analysis of the 3-D coordinates of the centroids of the retroreflective markers.

A calibration frame of known proportions was used to define the 3-D area in which data were collected. There were 16 spheres hung in 4 strings in a cubic arrangement, and a minimum of 6 markers on the frame must be viewed by at least 2 cameras to allow direct linear transformation of the coordinate points using an 11-parameter calculation.[12] The horizontal (x) axis, the vertical (y) axis, and the anterior-posterior (z) axis were defined, with the vertical axis being true vertical. The expected accuracy of the data collected in the area defined by the calibration frame would be approximately 1 part in 1,500, or >0.07%.[13]

A head-holder was used to comfortably restrain the subject's head so that any displacement of reference marker positions was not thought to be due to head movement. The head-holder consisted of a metal jig to which a disposable wooden bite bar was attached. Subjects were asked to gently bite on the bite bar to stabilize the head. Subjects were allowed adequate rest between trials and were allowed practice trials to ensure familiarity with the movements.

Following data collection, each frame of data was viewed to label the marker positions and ensure continuity of the marker trajectories. The data were then smoothed at 5 Hz, which was the frequency determined by the residual analysis and curve fitting techniques described by Winter.[14]

The reference points were determined for each axis and each movement by examining the mean displacement of the proposed reference points at rest and then during movement. In order to determine the range of motion of the reference marker for each expression, the minimum displacement was subtracted from the maximum displacement to give a total displacement in each of the 3 axes of movement. Points were defined as still, if during facial expression the range of movement of those points was not more than 2 standard deviations from the resting mean. By this calculation, no points on the face were found to be "still" in all 3 dimensions during the test protocol of facial expressions. So, the points that moved the least in the x, y, and z axes were investigated. Of the points that moved the least, the reference points chosen for each facial movement had the lowest mean 3-D displacement, and had the most frequently occurring lowest displacement in each axis. When 2 points equally satisfied these criteria, then the point with the lowest standard deviation for the mean 3-D displacement was chosen as the reference point.

RESULTS

Facial reference points were derived mathematically from the trials that were performed in a head-holder. No points were found to be still during facial expression. The displacements for the chosen reference points are listed in Table 1. The point 3 cm inferior to the mid–lower lip was chosen for forehead raise and tight eye closure, the left tragus was chosen for nose wrinkle, and the soft tissue nasion was chosen for maximum smile, pout, and lips pulled

TABLE 2. MEAN DISPLACEMENTS OF INDIVIDUAL AXES AND 3-D COMBINED DISPLACEMENTS OF FACIAL REFERENCE POINTS FOR AVERAGE OF REST TRIALS 1 AND 2

	Horizontal Axis (mm)	*Vertical Axis (mm)*	*Anterior-Posterior Axis (mm)*	*3-D Combined (mm)*
Nasion	0.24	0.17	0.23	0.37
Left tragus	0.32	0.27	0.38	0.57
3InfML lip	0.22	0.21	0.27	0.41

down.

On Table 1, during facial movements, the mean 3-D displacements of the chosen points range from 0.99 mm for the 3-cm-inferior mid–lower lip marker during forehead raise and 2.60 mm for the soft tissue nasion marker during pout. The lowest mean individual axis displacement (0.26 ± 1.28 mm) was recorded for the vertical axis of the 3-cm-inferior mid–lower lip marker during forehead raise. The highest displacement (2.11 ± 2.09 mm) was for the 3-cm-inferior mid–lower lip marker during tight eye closure.

The largest amount of overall mean reference marker movement occurred in the anterior-posterior axis (mean 1.53 mm) for the majority of movements, except for tight eye closure, which has a higher individual axis mean vertical displacement. The vertical axis had the second highest overall reference marker displacement, and the horizontal axis the lowest overall mean displacement.

The movement of the reference markers was examined at rest to determine the amount of system noise and physiological tremor present. There were 2 rest trials, rest 1 and rest 2, performed at the beginning and the end of the head-holder movement sequence. The mean individual axis displacements and 3-D combined displacements of the reference markers at rest for these 2 trials are presented in Table 2.

During rest trials, the mean displacement of the individual axes of the facial reference points chosen for this study, as shown in Table 2, ranged from 0.17 mm, for the vertical axis of the soft tissue nasion, to 0.38 mm, for the left tragus in the anterior-posterior axis. The combined 3-D displacement ranged from 0.37 mm, for the soft tissue nasion, to 0.57 mm for the left tragus.

DISCUSSION

The establishment of facial reference points from which facial movement may be tracked is fundamental to the accuracy of future displacement data. This study examined facial reference points and found that there was no place on the face that was completely still during facial expression. However, places of minimal movement on the face were determined for each individual expression. This movement was investigated by examining the displacement of the facial reference markers with the face at rest and during facial movement. Reasons for finding no completely still points may be motion analysis system error, physiological tremor, a small amount of skin movement, or some combination of these. Slight head-holder movement during facial expressions also may have occurred if the subject bit down hard on the bite bar. System error and physiological tremor were measured by the combined 3-D displacement of the facial reference points at rest, ranging from 0.37 mm, for the soft tissue nasion, to 0.57 mm, for the left tragus (Table 2). Although the reference markers only moved a relatively small amount, the overall displacement of the markers during facial movement is also relatively small.[15] Reference marker movement must be taken into account when examining future displacement data.

CONCLUSIONS

The displacement of facial reference points was examined during facial expressions, and it was found that

1. There were no completely still points on the face.
2. Reference points were determined with very small movements for each individual expression.
3. Small reference point movements were thought to be the result of system noise, physiological tremor, skin movement, or slight head-holder movement during facial expressions.

Future studies of the displacement of the markers during facial movement in both normal subjects and patients with facial nerve paralysis may use these reference points, taking into account the contribution of the reference point displacements to the overall facial movement.

ACKNOWLEDGMENTS — The authors acknowledge the assistance of the staff, particularly Ray Patton, of the School of Exercise and Sports Science, Faculty of Health Science, The University of Sydney, for their scientific and technical support.

REFERENCES

1. Wylie DR, Goodale MA. Left-sided oral asymmetries in spontaneous but not posed smiles. Neuropsychologia 1988;26:823-32.

2. Stussi E, Hanschin S, Frey M. Quantification of facial asymmetries. A method of objectifying motor impairments following facial nerve injuries. A pilot study. Biomed Tech (Berlin) 1992;37:14-9.

3. Tanaka H, Murata K, Isono M, et al. Quantitative analysis

of facial motions. In: McCafferty G, Coman W, Carroll R, eds. Conference Proceedings, XVI World Congress Otorhinolaryngol Head Neck Surg, Sydney, Australia, 1997:119-23.

4. Kawamoto M, Murata K, Isono M, Tanaka H, Azuma H. Computerised quantitative analysis of facial motions. In: McCafferty G, Coman W, Carroll R, eds. Conference Proceedings, XVI World Congress Otolaryngol Head Neck Surg, Sydney, Australia, 1997:103-6.

5. Coulson SE, Croxson GR, Gilleard WG. Quantification of the three dimensional displacement of normal facial movement. A pilot study. Aust J Otolaryngol 1996;2:344-8.

6. Ferrario VF, Sforza C, Miani A, Tartaglia G. Craniofacial morphometry by photographic evaluations. Am J Orthod Dentofacial Orthop 1993;103:327-37.

7. Fields MJ, Peckitt NS. Facial nerve function index: a clinical measurement of facial nerve activity in patients with facial nerve palsies. Oral Surg Oral Med Oral Pathol 1990;69:681-2.

8. Larrabee WF, Maupin G, Sutton D. Profile analysis in facial plastic surgery. Arch Otolaryngol 1985;111:682-7.

9. Peckitt NS, Walker RV, Barker GR. The facial nerve function coefficient: analysis of 100 subjects. J Oral Maxillofac Surg 1992;50:338-9.

10. Coulson SE, Croxson GR. Assessing physiotherapy rehabilitation outcomes following facial nerve paralysis. Aust J Otolaryngol 1995;2:20-4.

11. Nigg BM, Herzog W. Biomechanics of the musculoskeletal system. New York, NY: John Wiley & Sons, 1994.

12. Expert Vision reference manual. Santa Rosa, Calif: Motion Analysis Corporation, 1989.

13. Walton JS. The accuracy and precision of a video-based motion analysis system. In: Proc 30th Int Tech Symp Optical Optoelectronic App Sc Engineering, High Speed Photog, Videog Photonics IV, 693, San Diego, Calif, 1986:17-22.

14. Winter DA. Biomechanics and motor control of human movement. 2nd ed. Toronto, Canada: John Wiley & Sons, 1990: 36-43.

15. Coulson SE, Croxson GR, Gilleard WL. Quantification of the three dimensional displacement of normal facial movement and following facial nerve paralysis. In: Conference Proceedings, VIII Int Symp Facial Nerve, Matsuyama, Japan, 1997: 146.

≈

MENIERE'S DISEASE

The Fourth International Symposium on Meniere's Disease will be held in Paris, France, April 11-14, 1999. For information, contact Administrative and Scientific Secretariat, SOCFI/MENIERE '99, 14 rue Mandar, 75002 Paris, France; telephone 33 (0) 1 44 88 25 25; fax 33 (0) 1 40 26 04 44; e-mail fournier@socfi.fr.

Ann Otol Rhinol Laryngol 108:1999

MULTIFOCAL CHOLESTEATOMA OF THE EXTERNAL AUDITORY CANAL FOLLOWING BLAST INJURY

MICHAEL WOLF, MD
LELA MEGIROV, MD
JONA KRONENBERG, MD
TEL-AVIV, ISRAEL

Posttraumatic cholesteatoma of the external auditory canal is a rare condition that may present years after the original injury. A unique case of multifocal cholesteatoma of the external auditory canal following blast injury is presented and discussed.

KEY WORDS — blast injury, cholesteatoma, external ear canal.

Cholesteatoma of the external auditory canal (EAC) is an uncommon condition,[1] usually related to ear surgery, congenital stenosis of the canal, obstruction by osteoma or other tumors, or keratosis obturans.[2,3] At times, acquired atresia of the ear canal may develop following local infection and lead to an impacted squamous collection.[4] However, posttraumatic cholesteatoma of the EAC has rarely been described.[5] Unfortunately, blast injury has been not infrequently encountered in our practice, including its effects on middle ear structures.[6] Involvement of the EAC, however, has been rarely encountered.

CASE REPORT

A 19-year-old soldier was exposed to blast trauma in a combat situation. He complained of hearing loss and tinnitus in his right ear, accompanied by severe vertigo, nausea, and vomiting. Otoscopy revealed shrapnel wounds of undefined material and a second-degree burn involving the auricle in the area of the helix and cavitas conchae, with cerebrospinal fluid draining through a subtotal perforation of the tympanic membrane. Left-beating spontaneous nystagmus and positive Romberg and past-pointing tests to the right were evident. An audiogram demonstrated an essentially deaf right ear. A computed tomography scan demonstrated a longitudinal fracture of the temporal bone, with air-fluid levels in the mastoid air cells and middle ear cavity. The otorrhea stopped following a few days of complete bed rest, and the auricular wounds slowly healed. The disequilibrium gradually subsided over several weeks. Over a 6-month interval, multiple foci of cholesteatomatous lesions (pearls) developed on the inferior, posterior, and superior parts of the EAC (see Figure, A). The patient underwent surgery and the involved skin (see Figure, B) was replaced by a full thickness free skin graft with good results. Histologic examination demonstrated small epidermoid cysts of various sizes located just beneath the epithelium or deeper in the superficial dermis, lined by skin and containing keratin (see Figure, C). Myringoplasty was successfully performed as a second stage, 6 months later, revealing a missing incus and a luxated stapes.

DISCUSSION

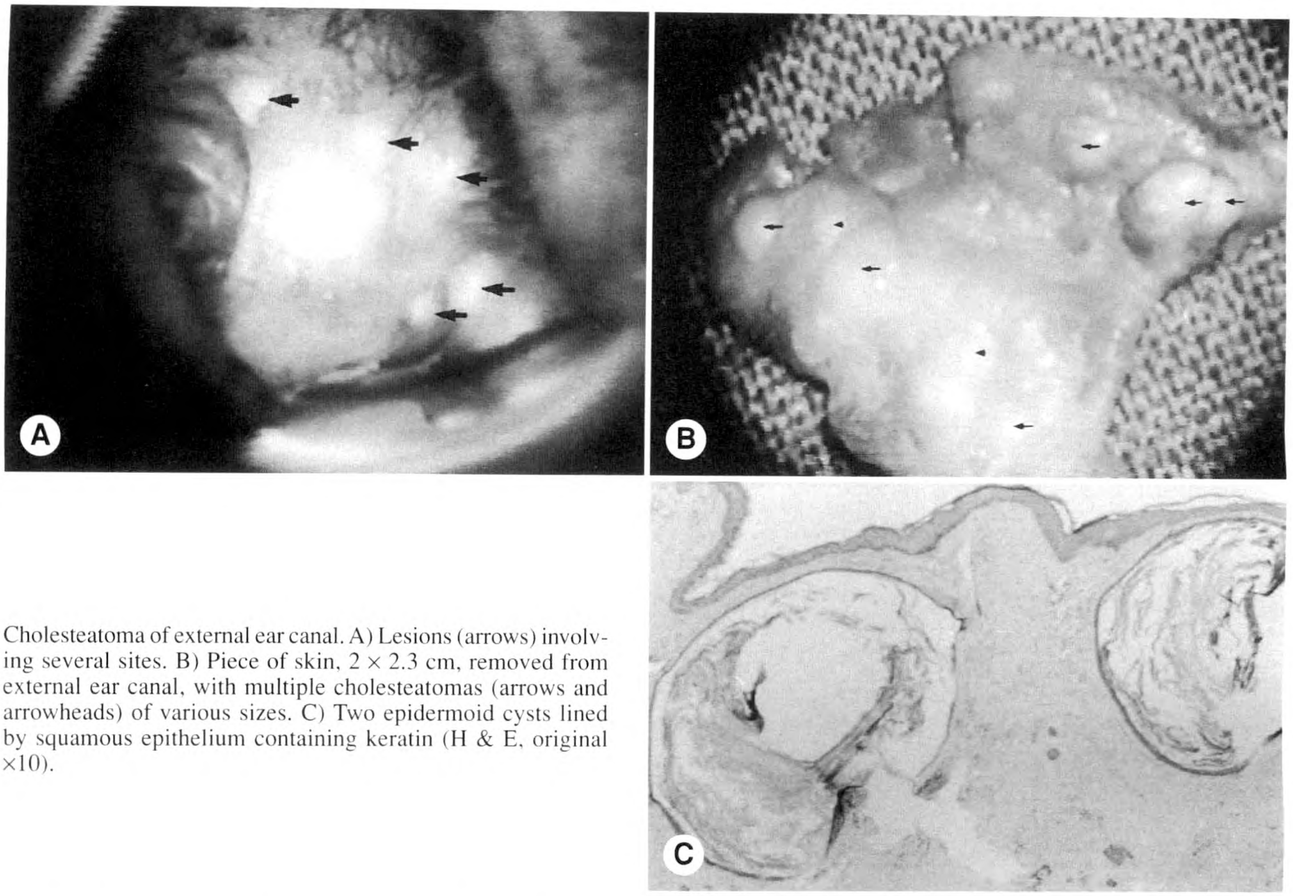
Posttraumatic cholesteatoma is histologically identical to any cholesteatoma of the EAC, but its clinical characteristics differ significantly by its late presentation, unusual location, and growth patterns.[5,7,8] In reviewing the literature, Brookes and Graham[5] found only 8 such cases reported previously, mainly in the German literature. They identified 2 principal growth patterns. One is by direct implantation of epithelium into a fracture line, into a gunshot wound, or into other missile sites of injury.[7,9] In the latter situation, fragments of foreign bodies may also be implanted, with the likelihood of induced secondary infection. The other pattern is by posttraumatic stenosis of the meatus or by osseous distortion due to the direct impact of a gunshot trauma with cholesteatoma formation medial to the obstruction.[10] Farrior[11] suggested that repeated local trauma caused by cotton-tipped applicator abusers may also induce cholesteatoma of the EAC.

Treatment depends on the extent of the lesion. Debridement and skin grafting seems sufficient for limited lesions. That the tympanic membrane and cavity are seldom involved in nontraumatic cholesteatoma of the EAC suggests the option of a more conservative approach with functional reconstruction.[5,7] However, the unusual growth patterns of posttrau-

---

From the Department of Otorhinolaryngology–Head and Neck Surgery, Sheba Medical Center, Tel-Hashomer, and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

CORRESPONDENCE — Michael Wolf, MD, Dept of Otorhinolaryngology–Head and Neck Surgery, Sheba Medical Center, Tel-Hashomer, 52621, Israel.



Cholesteatoma of external ear canal. A) Lesions (arrows) involving several sites. B) Piece of skin, 2 × 2.3 cm, removed from external ear canal, with multiple cholesteatomas (arrows and arrowheads) of various sizes. C) Two epidermoid cysts lined by squamous epithelium containing keratin (H & E, original ×10).

matic cholesteatoma in a normal aerated mastoid cavity may dictate rather extensive intervention.

In a series of 147 ears that sustained blast injury, Kronenberg et al[6] described cholesteatoma (invasive) and pearl (confined) lesions involving the middle ear in 4.8% and 1.8%, respectively. They suggested that reconstructive procedures be postponed for 1 year following the trauma so that any growth of squamous epithelium could be detected. Posttraumatic lesions have, however, presented up to 24 years following the insult.[8]

Involvement of the EAC has not been encountered in several series reporting on blast injury.[12-14] In this particular case, fracture of the temporal bone and shrapnel wounds may have induced the cholesteatoma formation. Multifocal seeding of keratin cysts covered a relatively wide area of the external ear canal without a foreign body reaction. It seems most likely to represent the implantation theory of cholesteatoma formation.

REFERENCES

1. Anthony PF, Anthony WP. Surgical treatment of external auditory canal cholesteatoma. Laryngoscope 1982;92:70-5.

2. Piepergerdes JC, Kramer BM, Behnke EE. Keratosis obturans and external auditory canal cholesteatoma. Laryngoscope 1980;90:383-91.

3. Holt JJ. Ear canal cholesteatoma. Laryngoscope 1992; 102:608-13.

4. Bonging P, Tos M. Post-inflammatory atresia of the external auditory canal. Acta Otolaryngol (Stockh) 1975;79:115-23.

5. Brookes GB, Graham MD. Post-traumatic cholesteatoma of the external auditory canal. Laryngoscope 1984;94:667-70.

6. Kronenberg J, Ben-Shoshan J, Modan M. Blast injury and cholesteatoma. Am J Otol 1988;9:127-30.

7. McKennan KX, Chole RA. Post-traumatic cholesteatoma. Laryngoscope 1989;99:779-82.

8. Bottrill ID. Post-traumatic cholesteatoma. J Laryngol Otol 1991;105:367-9.

9. Freeman J. Temporal bone fractures and cholesteatoma. Ann Otol Rhinol Laryngol 1983;92:558-60.

10. McKennan KX, Chole RA. Traumatic external auditory canal atresia. Am J Otol 1992;13:80-1.

11. Farrior J. Cholesteatoma of the external ear canal. Am J Otol 1990;11:113-6.

12. Pahor AL. The ENT problems following the Birmingham bombings. J Laryngol Otol 1981;95:399-406.

13. Kerr AG. Trauma and the temporal bone. The effects of blast on the ear. J Laryngol Otol 1980;94:107-10.

14. Sudderth ME. Tympanoplasty in blast-induced perforation. Arch Otolaryngol 1974;99:157-9.

Ann Otol Rhinol Laryngol 108:1999

VESTIBULAR RESPONSES OF NORMAL AND HYDROPIC EARS OF THE GUINEA PIG TO MIDDLE EAR PRESSURE APPLICATION

YASUHIKO SAKIKAWA, MD
CONRAD WALL III, PHD
ROBERT S. KIMURA, PHD
BOSTON, MASSACHUSETTS

The pressure in the middle ears of normal and hydropic guinea pig ears was increased, and nystagmographic recordings were compared. Two-month unilateral hydropic guinea pigs and normal control guinea pigs underwent pressure treatments in which pressure was introduced into the middle ear. Significantly lower pressure was needed to elicit nystagmus in hydropic ears (mean 1.00 psi or 70.3 cm H_2O) compared with normal control ears (mean 1.27 psi or 89.3 cm H_2O). All of the normal control guinea pigs showed fast phase nystagmus toward the pressure-applied side, while hydropic guinea pigs showed nystagmus toward the normal ear. The duration of nystagmus was slightly longer in hydropic animals than in normal control animals. The slow phase velocity was slightly higher in the hydropic guinea pigs. Histologic examination revealed that the vestibular sensory cells remained normal and that changes in the organ of Corti were similar between the hydropic ears with and without pressure treatment at equal survival times.

KEY WORDS — hydrops, middle ear pressure, nystagmus, vestibular response.

INTRODUCTION

The inner ears of Meniere's disease cases show endolymphatic hydrops which indicates that a pressure increase in the endolymph compartment has occurred. Densert et al[1] reported that exposure of patients with Meniere's disease to underpressure in a pressure chamber resulted in improved hearing at low frequencies and relief of subjective symptoms. The mechanism is based on reducing ambient pressure to induce relative overpressure in the middle ear. A subsequent study showed that local application of overpressure to the middle ear improved hearing in Meniere's disease patients.[2] These reports support the idea that pressure in the inner ear can be manipulated by increasing or decreasing pressure in the middle ear cavity. While it has been suggested that pressure change in the middle ear causes a vestibular response[3,4] and alters the activities of primary vestibular neurons,[5-7] the mechanism by which this overpressure affects the inner ear is still not clear. In the present study, the vestibular responses and histologic changes caused by increased middle ear pressure in normal and hydropic ears were compared.

MATERIALS AND METHODS

Twenty-eight Duncan-Hartley albino guinea pigs, each weighing 250 to 350 g, were included in this experiment. These animals were divided into 3 groups: 1) 15 animals underwent endolymphatic duct obliteration on the right side to produce hydrops[8]; 12 of these animals underwent pressure treatment 2 months later, and the remaining 3 animals underwent treatment 1 day later; 2) 8 normal animals were treated similarly with pressure and served as controls; and 3) 5 control hydropic specimens were obtained from the guinea pig temporal bone collection of the ENT Electron Microscopy Laboratory, Massachusetts Eye and Ear Infirmary. The histologic results from the 2-month hydropic ears with pressure treatment were compared with those from 5 hydropic ears of equal survival time that did not undergo pressure treatment.

Under intraperitoneal Nembutal anesthesia, a plastic tube was inserted into the superior-posterior part of the right bulla, 2 mm deep, and was fixed tightly with dental cement. This tube was connected to a pressure chamber (B-II, Reimers Engineering, Alexandria, Va) via a Heise digital pressure indicator (901A, Heise, Newtown, Conn), allowing pressure to be introduced into the middle ears of awake animals placed outside the chamber in a lighted room. The rate of the pressure change was 1.0 psi (70.3 cm H_2O) per 15 seconds. Pressure was increased to 1.5 psi (105.5 cm H_2O), even if nystagmus appeared at a lower pressure, and was maintained for 10 minutes. The eustachian tube was presumably patent or

---

From the Department of Otology and Laryngology, Harvard Medical School, and the Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. This work was supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant R01 DC00073. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Massachusetts Eye and Ear Infirmary.

CORRESPONDENCE — Robert S. Kimura, PhD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

TABLE 1. PRESSURE NEEDED TO ELICIT NYSTAGMUS AND DURATION OF NYSTAGMUS

	Normal (N = 6)		*Hydrops (N = 11)*	
	Mean	*Range*	*Mean*	*Range*
Pressure level that elicits nystagmus (psi)	1.27	1.2-1.4	1.00	0.9-1.2
Duration (s)	15.0	7-20	25.9	13-48

forced open by direct middle ear pressure application. Tube insertion into the bulla instead of the external auditory canal provides firmer tube attachment — to the bone, rather than to the skin — for a long period of time. In a separate study, the pressure in the middle ear was measured by inserting a second tube connected to the digital pressure indicator and was compared with the pressure reading of the pressure chamber. During the pressure treatment, the middle ear pressure and the pressure reading of the pressure chamber increased concomitantly and remained stable 3 to 4 minutes or longer. Nystagmus appeared at the beginning of the treatment and lasted for about 2 minutes. Pressure treatments were performed at room temperature (22°C to 25°C). Electronystagmography (ENG) was performed on each animal on the first and second days of the pressure treatment in order to investigate the different responses of hydropic and normal guinea pigs to the increased middle ear pressure. Monocular horizontal eye movements were recorded with silver chloride surface electrodes attached at both corners of the eye, with a grounding electrode on the forehead. Recordings were calibrated by moving the animals ±10° with eyes open in the light. Animals were rotated slowly back and forth in the yaw axis of the head at approximately 2°/s to 3°/s in the light while they viewed a full field visual surround that was meant to activate the optokinetic system in synergy with the vestibulo-ocular reflex to produce a completely compensatory movement of the eyes. In some experiments, we visually observed the eye movements to verify compensatory slow components. The ENG recorder was used with a 0- to 30-Hz bandpass. We calibrated the device using 100°/s to 250°/s triangle waves and determined that the filter introduced a 10% to 20% error in slope determination over this range. The error for slower velocities was correspondingly less. The pressure level at which nystagmus appeared and the duration of the nystagmus were recorded. This experiment was repeated daily for 10 days in order to examine the histologic changes due to the pressure application; nystagmus was not recorded in the period between the 3rd and 10th days of pressure application. The animals were painlessly sacrificed immediately after the last treatment, and the temporal bones, except those from the 1-day endolymphatic duct blockage series, were removed and processed in celloidin for histologic examination under light microscopy. Statistical analysis was performed with Student's *t*-test.

RESULTS

Nystagmus was observed during pressure treatments in 11 of the 12 two-month hydropic guinea pigs and 6 of the 8 control guinea pigs. The pressure needed to elicit nystagmus in hydropic guinea pigs (mean 1.00 ± 0.12 psi) was significantly less than that in control guinea pigs (mean 1.27 ± 0.15 psi). The duration of nystagmus was slightly longer in hydropic guinea pigs (mean 25.9 ± 13.18 seconds) than in normal animals (mean 15.0 ± 5.06 seconds), but the difference was not statistically significant (Table 1). For purposes of analysis, nystagmus was recorded with eyes open in the dark. The placement of the electrodes at the canthi resulted in recording only the horizontal component of the movement. We also made visual observation of the movements in the light, where we observed typical horizontal-rotary movements. The ENG recordings of normal control guinea pigs showed that the direction of fast phase nystagmus was toward the pressure-applied side. The ENG recordings of hydropic guinea pigs showed that the direction of fast phase nystagmus was usually toward the normal ear; however, in a few animals, the nystagmus changed direction from toward the normal ear to toward the pressure-applied ear during the nystagmus recording session. In both control and hydropic guinea pigs, nystagmus appeared 8 to 15 seconds after initiation of the pressure application; the nystagmus increased in amplitude and gradually disappeared after 10 to 30 seconds (Fig 1). One day after blockage of the endolymphatic duct, the direction of nystagmus and the pressure required to induce nystagmus were similar to those of the normal animals.

The mean of the absolute value of the slow phase velocity (SPV)[9] of nystagmus was significantly larger in the hydropic guinea pigs than in the controls. The maximum of the absolute value of the SPV was larger in the hydropic guinea pigs than in the controls, but the difference was not statistically significant (Table 2). The SPV also demonstrated that the direction of nystagmus in hydropic and control guinea pigs was different and that the duration of nystagmus was longer in hydropic guinea pigs (Fig 2).

Under histologic examination, the saccular membrane was attached to the stapes footplate and the distended utricular membrane in all hydropic ears; however, the magnitude of hydrops with and without pressure treatment was similar (Fig 3). All utricles

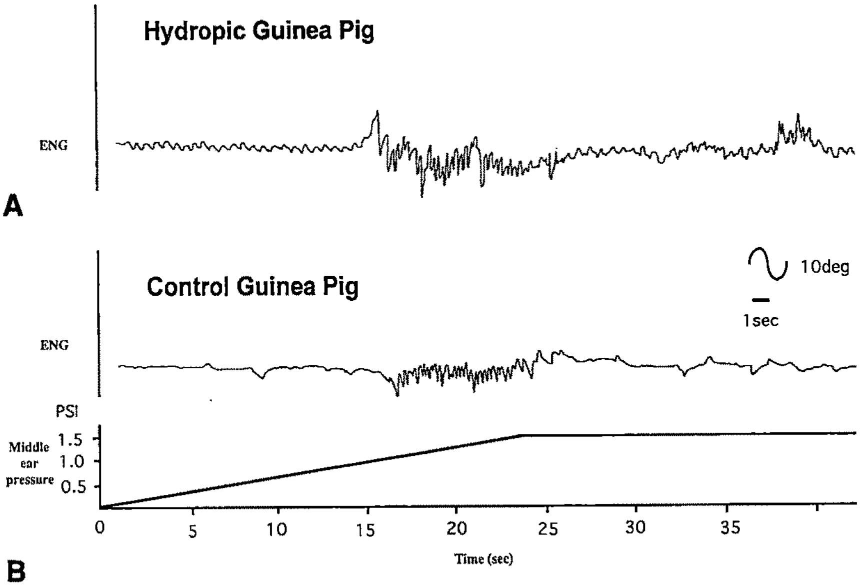


Fig 1. Electronystagmography (ENG) recordings from A) hydropic and B) control guinea pigs. Direction of fast phase nystagmus was toward pressure-applied side in control guinea pigs and away from pressure-applied side in hydropic guinea pigs.

showed endolymphatic hydrops. The ampullae did not show obvious enlargement. Four of the 12 hydropic ears and 2 of the 8 normal ears showed collapse of Reissner's membrane in part of the cochlea. The histologic findings did not, however, correspond to the observed vestibular response. The neurovestibular sensory structures did not show any histologic changes. The auditory neurosensory structures and the stria vascularis demonstrated histologic changes in the hydropic ears with pressure treatment; however, these findings were also shown in the hydropic ears without pressure treatment. There were no histologic changes in the neurosensory structures in normal control ears with pressure treatment.

DISCUSSION

Since Hallpike and Cairns[10] demonstrated the distention of the endolymphatic system in temporal bones of Meniere's disease cases, an increase in endolymphatic pressure has been thought to be a cause of acute symptoms in Meniere's disease patients.[11] Although there is no proof for this hypothesis, increased middle ear pressure is known to induce vertigo and nystagmus.[1,4,12]

Our study shows that when middle ear pressure was applied, the direction of fast phase nystagmus was toward the tube-inserted side in the normal control guinea pigs, and toward the unoperated side in the hydropic guinea pigs. The mechanism of stimulating vestibular sensory cells by middle ear pressure application may be different in normal and hydropic ears. When middle ear pressure is increased in the normal ear, the firing rates of the lateral canal nerves are increased, whereas the nerves originating from the vertical canals respond only slightly.[5] Excitation of sensory cells occurs when the sensory ciliary bundle is displaced toward the kinocilium.[13] In the lateral canal, the kinocilia of sensory cells are oriented toward the utricle, and thus, the effective stimulation of sensory cells is caused by deflection of the cupula and sensory ciliary bundle toward the utricle. When pressure is applied to the middle ear, perilymph is displaced toward the opened end of the perilymph compartment: the cochlear and vestibular aqueducts. Displacement of perilymph and/or endolymph in the lateral canal may have occurred toward the utricle to induce excitation of sensory cells. Perilymph flow in the canal is believed to cause greater cupular displacement of the canal crista than that produced by endolymph alone.[14] An increase in perilymph pressure in the lateral canal induces nystagmus toward the pressure-applied side.[15] Our study of normal ears shows that pressure application to the middle ear, which is expected to increase perilymph pressure, caused development of nystagmus toward the same side. These findings suggest that perilymph displacement in the lateral canal may have induced cupular deflection toward the utricle, thus causing an increase in neural activity of the lateral canal nerves and nystagmus.

TABLE 2. MEAN AND MAXIMUM ABSOLUTE VALUES OF SLOW PHASE VELOCITY

	Normal (N = 6)		*Hydrops (N = 11)*	
	Mean	*Range*	*Mean*	*Range*
Mean SPV (°/s)	44.27	29-78	92.10	39-156
Maximum SPV (°/s)	114.6	60-225	185.0	128-262

In the hydropic ear, endolymph displacement may be a primary factor causing deflection of the cupula. Endolymph is more readily displaced by middle ear pressure application in the hydropic ear than in the normal ear, because the saccular membrane attaches

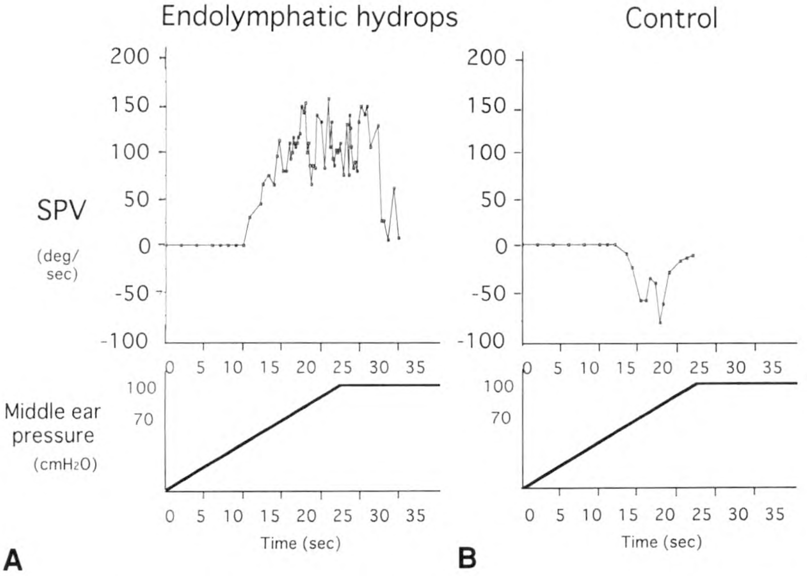


Fig 2. Slow phase velocity (SPV) in A) hydropic and B) normal control guinea pigs. Absolute value of SPV was slightly higher in hydropic guinea pigs than in controls. Direction of nystagmus in hydropic and control guinea pigs was different.

to the stapes footplate 2 months postoperatively. As the stapes is pushed inward by increasing middle ear pressure, endolymph will be displaced toward the saccular and utricular ducts, into the utricle and ampullae. The deflection of the cupula and sensory ciliary bundle is toward the canals from the utricle side. The effect in the lateral ampulla is inhibitory to sensory cells, possibly causing hyperpolarization of the cells and leading to decreased nerve firing.[13]

The vestibular responses of the animals that have had endolymphatic duct blockage for 1 day are not different from those of normal animals. Histopathologic study of our chronological hydropic temporal bone collection shows that the distended saccular membrane is not attached to the stapes footplate at 1 day, but that it begins to attach at about 2 weeks postoperatively. Thus, the blockage of the endolymphatic duct itself is not the cause of the change in direction of nystagmus, but the magnitude of endolymphatic hydrops is a contributing factor.

The otolithic organs are also expected to be stimulated by middle ear pressure application. The mechanism of this stimulation is complex, because the orientation of the kinocilium in the utricular macula is

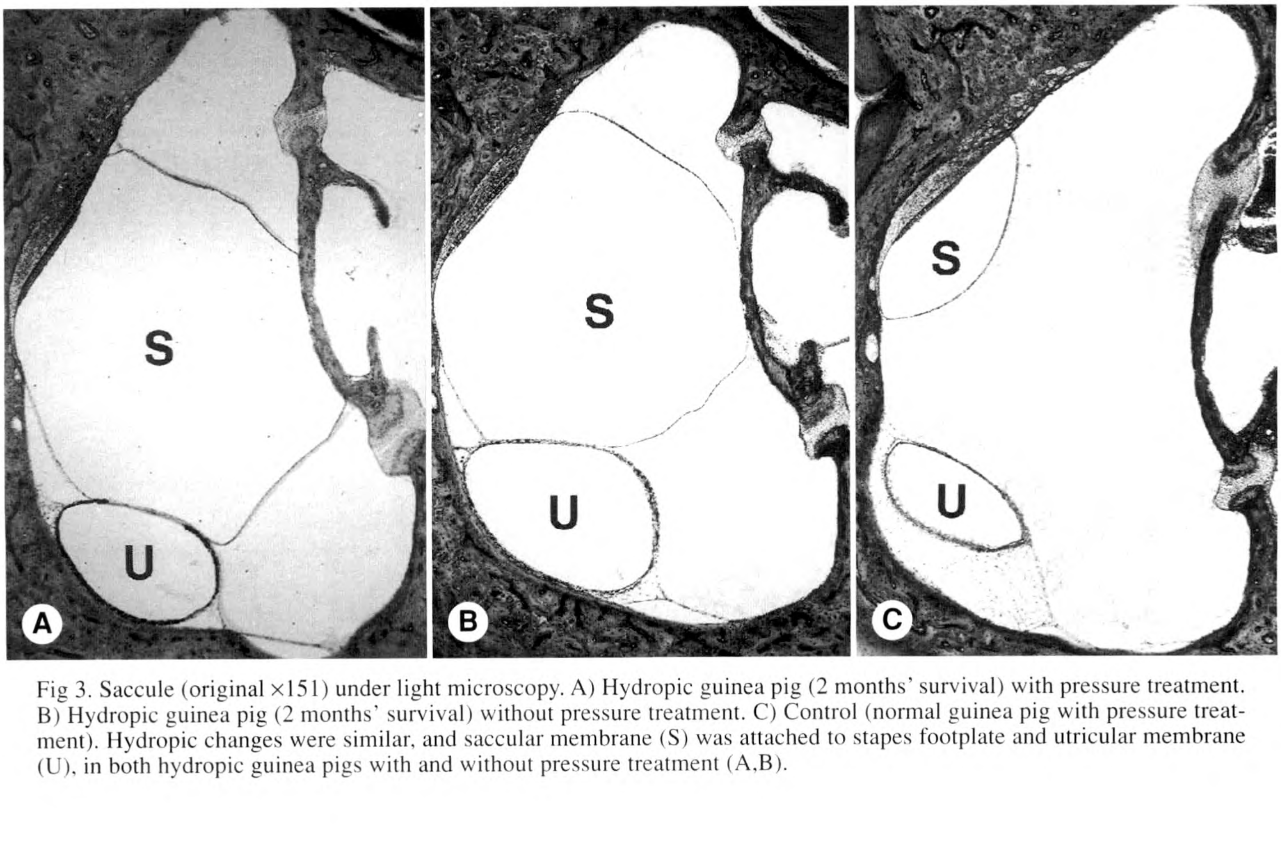


Fig 3. Saccule (original ×151) under light microscopy. A) Hydropic guinea pig (2 months' survival) with pressure treatment. B) Hydropic guinea pig (2 months' survival) without pressure treatment. C) Control (normal guinea pig with pressure treatment). Hydropic changes were similar, and saccular membrane (S) was attached to stapes footplate and utricular membrane (U), in both hydropic guinea pigs with and without pressure treatment (A,B).

toward the striola, while in the saccular macula the orientation is away from the striola.[13] Pressure induces endolymph displacement, but the direction of otolithic membrane or sensory ciliary bundle displacement cannot be determined, and thus, it is unknown which group of sensory cells in the macula or maculae is excited. Otolithic sense organs are more sensitive to an increase in middle ear pressure than are the canal organs[6]; this fact implies that pressure may cause the otoliths to deflect the ciliary bundle of the hair cells more readily than the cupula deflects them. Because endolymph can be displaced more easily in hydropic ears, due to the saccular membrane attachment to the stapes footplate, the sensitivity of sensory cells to middle ear pressure application can be enhanced. However, postural tests were not performed to determine this effect in this study.

The pressure required to induce a vestibular reaction in the normal guinea pig was 89.3 cm H2O, which is higher than that of the human (60 cm H2O).[12] Human ears are more sensitive to an external pressure increase than guinea pig ears. This difference in the pressure level may be related to the patency of the cochlear aqueduct in guinea pig ears in comparison to the frequently reduced patency shown in human ears[16] and/or to the site of pressure application. In hydropic guinea pigs, lower pressure (70.3 cm H2O) is needed to elicit nystagmus in comparison to normal guinea pigs. In these ears, because the saccular membrane is attached to the stapes footplate and utricular membrane, the cupula may be more readily displaced to produce nystagmus by application of lower middle ear pressure.

The prolonged nystagmus shown in hydropic animals may be due to larger displacement of the cupula and otolithic membrane, which may result in either slow recovery of these membranes to their normal positions or slow functional recovery of sensory cells. The duration of the increase in perilymph pressure is related to the patencies of the cochlear aqueduct and eustachian tube.[17] In this experiment, the patencies of these channels were not a factor, because their conditions were the same in both normal and hydropic animals.

The speed of the slow component of nystagmus (SPV) in response to middle ear pressure application was greater in hydropic animals than in normal animals. The SPV is an expression of the sensitivity of the vestibular sensory cells in the caloric test.[18] The caloric test was not performed in this study, but the SPV value on pressure application may be different. The high SPV value in the hydropic ears could be related to increased sensitivity of vestibular sensory cells to pressure and/or due to large endolymph volume displacement induced by the pressure application. This increased sensitivity is in accord with the lower pressure needed to elicit nystagmus in hydropic animals compared with normal animals. It is possible that the slow component velocity was overestimated due to electrooculographic calibration errors. While we tried to move the animal slowly during calibration in the light, we may have inadvertently moved too rapidly and thus not have gotten a completely compensatory eye movement response. This reduced gain during calibration would result in an overestimation of slow component velocity. Our visual observation of the eyes during calibration argues against this possibility.

The pressure increase in the inner ears of hydropic guinea pigs induced by tilting the animals so that their heads are positioned down is known to produce spontaneous nystagmus toward the normal ear.[19] This finding suggests that hydropic ears are pressure sensitive. In Meniere's disease, it is hypothesized that a sudden increase in endolymphatic pressure would distort and rotate the top portion of the lateral canal crista, leading to relative utriculofugal displacement of the cupula and thus producing paretic nystagmus.[20] When the membranous lateral canal is interrupted by plugging, pressure application into the side of the lateral canal lumen continuous to the ampulla produces nystagmus toward the pressure-applied ear; however, when pressure is applied into the side of the lateral canal lumen continuous to the utricle, the direction is reversed.[15] These observations support our hypothesis that the paretic nystagmus response to increase in middle ear pressure in hydropic animals is due to endolymph movement toward the ampulla from the utricular side.

Vestibular symptoms could be caused by fistula in either the endolymphatic or perilymphatic compartment in hydropic ears. The pressure of endolymph is higher than that of perilymph in hydropic cochleas, and the compliance of the distended Reissner's membrane is decreased.[21] Thus, when pressure is applied to the stapes, to which the distended saccular membrane is attached, the membrane can rupture. The development of nystagmus and dizziness in Meniere's disease patients is often attributed to membrane rupture. Although the paretic nystagmus shown in hydropic guinea pigs is consistent with the membrane rupture theory, the short duration of the nystagmus and the absence of membrane rupture in the histologic specimens argue against the theory.

Perilymph fistula could occur and initiate nystagmus when middle ear pressure is increased, but in this experiment it is unlikely that this happened. If perilymph fistula is the cause of vestibular symptoms, we should see the same type of nystagmus in both the normal and hydropic animals, but this did not occur. Histologic examination showed neither obvious tears in the round window membrane nor dislocation of the stapes footplate.

Histologic examination showed that 1.5-psi pressure application to the middle ear 10 minutes per day for 10 days caused no obvious adverse effects on cochlear and vestibular sensory cells in the normal and hydropic ears, perhaps due to the short period of pressure application. Cytologic changes could be observed by electron microscopy or immunohistochemical investigations.

In conclusion, this study indicates 4 specific vestibular parameters in response to increased middle ear pressure in hydropic animals compared with normal control animals: 1) the direction of nystagmus was toward the normal ear, 2) the pressure level that elicited nystagmus was lower, 3) the duration of nystagmus was slightly longer, and 4) the SPV was larger, indicating increased sensitivity of vestibular sensory cells to pressure. These characteristics of vestibular responses may be useful in diagnosing endolymphatic hydrops in animal ears, and possibly in Meniere's disease and other diseases.

REFERENCES

1. Densert O, Ingelstedt S, Ivarsson A, Pedersen K. Immediate restoration of basal sensorineural hearing loss using a pressure chamber. Acta Otolaryngol (Stockh) 1975;80:93-100.

2. Densert B, Densert O. Overpressure in treatment of Meniere's disease. Laryngoscope 1982;92:1285-92.

3. Nylen CO, Karlefors J. On pseudo-fistula. Acta Otolaryngol (Stockh) 1922;3:156-9.

4. Tjernström Ö. Middle ear mechanics and alternobaric vertigo. Acta Otolaryngol (Stockh) 1974;78:376-84.

5. Ito J, Naito Y, Honjo I. The influence of middle ear pressure on the vestibular nerve activity in cats. Acta Otolaryngol (Stockh) 1990;110:203-8.

6. Naito Y, Ito J, Tsuji J, Honjo I. The influence of middle ear pressure on the otolith system in cats. Arch Otorhinolaryngol 1988;245:321-4.

7. Suzuki M, Kitahara M, Kitano H. The influence of middle ear pressure changes on the primary vestibular neurons in guinea pigs. Acta Otolaryngol Suppl (Stockh) 1994(suppl 510):9-15.

8. Kimura RS. Experimental blockage of the endolymphatic duct and sac and its effect on the inner ear of the guinea pig. A study on endolymphatic hydrops. Ann Otol Rhinol Laryngol 1967;76:664-87.

9. von Gierke HE. Evaluation of tests for vestibular function. Aviat Space Environ Med 1992;63(suppl).

10. Hallpike CS, Cairns H. Observations on pathology of Meniere's syndrome. J Laryngol Otol 1938;53:625-54.

11. Tonndorf J. Endolymphatic hydrops: mechanical causes of hearing loss. Arch Otorhinolaryngol 1976;212:293-9.

12. Ingelstedt S, Ivarsson A, Tjernström Ö. Vertigo due to relative overpressure in the middle ear. An experimental study in man. Acta Otolaryngol (Stockh) 1974;78:1-14.

13. Flock Å. Sensory transduction in hair cells. In: Loewenstein WR, ed. Principles of receptor physiology. Berlin, Germany: Springer-Verlag, 1971:395-441. (Handbook of sensory physiology; vol 1.)

14. Anliker M, Buskirk WV. The role of perilymph in the response of the semicircular canals to angular acceleration. In: Graybiel A, ed. Fifth Symposium on the Role of the Vestibular Organs in Space Exploration. Washington, DC: NASA, 1973: 135-41.

15. von Baumgarten R, Boehmer G, Brenske A, Reiser M. A nonthermoconvective mechanism generating caloric nystagmus: similarities between pressure-induced and caloric nystagmus in the pigeon. In: Graham MD, Kemink JL, eds. The vestibular system: neurophysiologic and clinical research. New York, NY: Raven Press, 1987:51-9.

16. Wlodyka J. Studies on cochlear aqueduct patency. Ann Otol Rhinol Laryngol 1978;87:22-8.

17. Carlborg B, Farmer J Jr, Carlborg A. Effect of hypobaric pressure on the labyrinth. Acta Otolaryngol (Stockh) 1990;110: 386-93.

18. Henriksson NG. Speed of slow component and duration in caloric nystagmus. Acta Otolaryngol [Suppl] (Stockh) 1956 (suppl 125).

19. Andrews JC, Honrubia V. Vestibular function in experimental endolymphatic hydrops. Laryngoscope 1988;98:479-85.

20. Brown DH, McClure JA, Dounar-Zapolski Z. The membrane rupture theory of Meniere's disease — is it valid? Laryngoscope 1988;98:599-601.

21. Bohmer A. Hydrostatic pressure in the inner ear fluid compartments and its effects on inner ear function. Acta Otolaryngol Suppl (Stockh) 1993(suppl 507).

Ann Otol Rhinol Laryngol 108:1999

RAT EUSTACHIAN TUBE AND ITS MUSCULATURE

JEF J. S. MULDER, MD
WIM KUIJPERS, PHD
NIJMEGEN, THE NETHERLANDS

The objective of this study was to evaluate the anatomy of the eustachian tube (ET) of the rat and the paratubal musculature. Microdissection and serial sections were used. The ET consists of collapsible membranous and membranocartilaginous segments and a noncollapsible bony segment. Tubal muscles are attached to the collapsible part; the salpingopharyngeus muscle (SPM) is well developed and consists of 3 distinct groups of muscle fibers; the tensor veli palatini muscle (TVPM) consists of 2 functionally different groups of fibers, but only 1 group assists in opening the ET. Attachment of the fibers of the SPM and TVPM that are involved in tubal opening is confined to the dorsal portion of the ET. This finding, together with the earlier observation that this part is mainly lined by squamous epithelium, strongly suggests that the dorsal part has a ventilatory function. The ventral portion of the ET, which is lined by ciliated-secretory epithelium and lacks the attachment of muscle fibers that can dilate the lumen, is assumed to serve clearance. The anatomic position of the levator veli palatini muscle suggests that this muscle contributes to the protective function of the ET. These findings are discussed with regard to the ET in humans.

KEY WORDS — clearance, eustachian tube, musculature, rat, ventilation.

INTRODUCTION

To cope with the divergent functions of ventilation, clearance, and protection of the middle ear, the eustachian tube (ET) is equipped with a specialized mucosa, various paratubal supporting structures, and paratubal muscles.[1] At present, there is no detailed concept of an anatomically based mechanism of middle ear ventilation and drainage. Although there is consensus on the general morphology of the ET[2-5] in the human, controversy exists on the fine structural relationships between paratubal muscles and cartilage and the tubal mucosa.[2,4,6-8] The tensor veli palatini muscle (TVPM) is generally considered to be the primary dilator of the ET[3,9,10] in humans, but there is a lack of understanding of the role of other paratubal muscles and the relationship between middle ear ventilation and other pharyngeal activities.[2,5,11-16] Studies on experimental animals can contribute to a better understanding of ET physiology because of their better accessibility. However, most attention has been focused on ET pathophysiology in relation to the development of otitis media. Studies on experimental animals to define the normal anatomy and physiology of the ET have only been performed incidentally, and the structural relationships between the paratubal structures and the tube have not been adequately described.[3,10,17-19]

In the present study on the rat, the tubal musculature and its relationship to the membranous tube and the framing bone and cartilage were investigated by a combined approach of microdissection and histologic techniques. This study is a continuation of an earlier study on the features of the epithelial lining of the ET in this animal.[20] The rat has been shown to be an appropriate model for studying otitis media with effusion induced by interfering with the paratubal musculature.[21,22]

METHODS

For this study, 20 adult Wistar rats (body weight 150 g) were used: 10 for microdissection and 10 for light microscopy studies. All the animals were painlessly sacrificed by an intracardiac injection of pentobarbital sodium and subsequently decapitated.

For staged microdissection, 5 fresh and 5 formaldehyde-fixed skulls were used. Dimensions were derived from the fresh specimens. Microdissection was performed by a dorsal and a ventral approach under the operating microscope at high magnification. To facilitate the identification of the different tissues during dissection, the exposed tissues were stained for a short time in a solution containing toluidine blue (0.7%), fuchsin (1.3%), and ethanol (30%).

For light microscopy studies, a tissue specimen containing middle ear, ET, and adjacent structures was dissected en bloc and fixed in phosphate buffered (0.1 mol/L; pH 7.4) formaldehyde (4%) for 48 hours. After decalcification in ethylenediaminetetraacetic acid (10%; pH 7.4), the specimens (n = 20) were trimmed to an appropriate size, dehydrated in graded alcohols, and embedded in paraffin or glycol methacrylate. Serial sections were made in coronal (n = 8) or sagittal planes (n = 8) or in a dorsoventral plane along the longitudinal axis of the tube (n = 4).

From the Department of Otorhinolaryngology, University of Nijmegen, Nijmegen, the Netherlands.

CORRESPONDENCE — Wim Kuijpers, PhD, University Hospital, Dept of Otorhinolaryngology, University of Nijmegen, Ph. van Leydenlaan 15, NL 6500HB Nijmegen, the Netherlands.

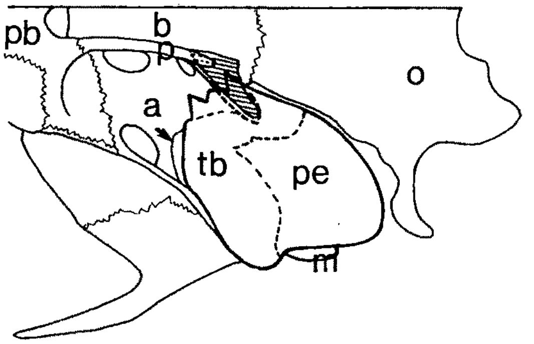


Fig 1. Drawing of ventral aspect of caudal part of rat skull, showing anatomic position of eustachian tube (dashed area). a — greater wing of sphenoid (alisphenoid) bone; b — basisphenoid bone; m — external meatus; o — occipital bone; p — pterygoid process; pb — palatal bone; pe — petrosal part of temporal bone; tb — tympanic part of temporal bone; arrow — petrotympanic fissure.

Paraffin sections (7 µm) were stained either routinely with toluidine blue, or with Weigert's method for elastic fibers, or with Van Gieson's method for the simultaneous demonstration of collagen and elastic fibers. Glycol methacrylate sections (2 µm) were routinely stained with toluidine blue.

RESULTS

The rat ET is a roughly funnel-shaped structure with a collapsed widened part and a short stalk with an open lumen. In the histologic sections, the collapsed part often showed an open lumen, but this was artificially induced by the tissue processing. The tube is 4 mm long (mean 4.0 mm, SD 0.14, n = 5) and runs in a laterocaudal direction from the nasopharynx to the middle ear. The anatomic position of the tube in the skull is shown in Fig 1. The straight rostral wall makes an angle of about 35° with the sagittal plane. The caudal wall is curved, and the angle with the sagittal plane is more obtuse. The nasopharyngeal opening consists of a curved slit (mean length 2.5 mm, SD 0.11, n = 6) that is situated in the lateral wall of the posterior part of the nasopharynx. The slit is normally closed except for the rostral part. The distance from the rostral border of the orifice to the posterior margin of the hard palate is about 4 mm. The distance from the caudal border to the nasopharyngeal hiatus is about 1.5 mm. The nasopharyngeal opening is situated at a lower level than the tympanic orifice (decline 15° to 20° with respect to the plane of the hard palate). The tympanic orifice is situated in the dorsomedial part of the tympanic part of the temporal bone. This bone, together with the petrosal part, forms the wall of the middle ear cavity (bulla). The middle ear is fairly loosely attached to the adjacent bones of the skull, and a large fissure (petrotympanic fissure) is present between the bulla and the caudal rim of the greater wing of the sphenoid (Fig 1). On the basis of the shape of the lumen and the paratubal structures, different segments can be distinguished: a medial, fully membranous, pharyngeal part (mean length 1.3 mm, SD 0.11, n = 7), an intermediate part (mean length 1.7 mm, SD 0.09, n = 7) in which the tube is framed to a variable extent by elastic cartilage and bone, and a lateral or tympanic part (mean length 1.0 mm, SD 0.07, n = 7) in which the lumen is completely framed by bone and cartilage.

The lumen in the tympanic segment, which is circular in cross section, is bordered dorsally by a caudolaterally directed, curved, sulcuslike bony process, arising from the basisphenoid and bordered on the remaining sides by a rostromedially directed process of the tympanic bone. Irregularly shaped cartilage is interposed between the mucosa and bone. At the tympanic orifice, the cartilage borders only the rostral lumen, but mediad, an increasing area of the lumen becomes framed by cartilage, and at the end of the tympanic segment, the whole mucosa is framed by cartilage except for a small area on the ventral side (Fig 2A).

The intermediate segment begins at the site in which the tube develops a slitlike ventral extension through the gap in the cartilaginous ring (Fig 2A). Toward the nasopharynx, this extension further enlarges in a caudal direction, giving the tube a crescentic appearance (Fig 2B,C). Subsequently, this typical shape gradually disappears and the tube flattens (Fig 2D-F). Initially, the ventral extension is completely framed by the medial process of the tympanic bone (Fig 2A,B), but toward the nasopharynx, the bony process gradually grows smaller and the exposed ventral wall of the tube becomes supported by the levator veli palatini muscle (LVPM) and the salpingopharyngeus muscle (SPM; Fig 2C-F).

The dorsorostral part of the lumen of the intermediate segment, which forms the continuation of the lumen of the tympanic segment, is surrounded by C-shaped cartilage (Fig 2B,C). The mucosa is tightly attached to the cartilage. Toward the nasopharynx, the cartilage gradually decreases in size (Fig 2D) and thereafter disappears (Fig 2E,F). Simultaneously, the lumen narrows and the luminal cross section changes from a circular to a slitlike configuration. The dorsorostral aspect of the cartilage is framed by a curved extension of the basisphenoid (Fig 2B-D). Caudally, the tube, including the caudal lamella of the cartilage, is bordered by a large seromucous gland, and it further increases in size toward the nasopharynx (Fig 2B-F).

In the nasopharyngeal segment, the tube is nearly

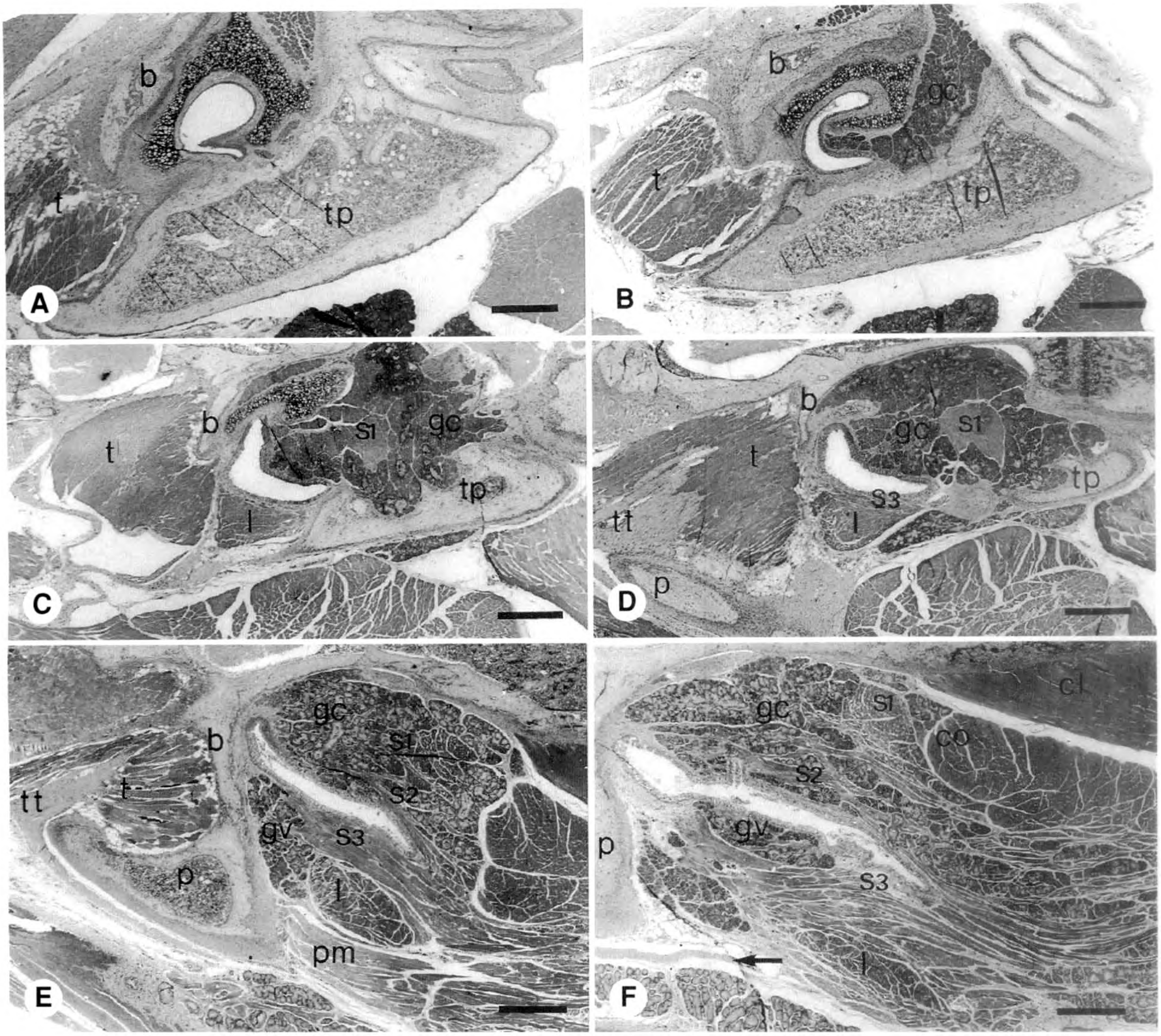


Fig 2. Sagittal sections from lateral to medial showing cross sections of eustachian tube lumen and paratubal structures (toluidine blue). Bars — 500 μm; b — basisphenoid bone; gc — caudal gland; gv — ventral gland; l — levator veli palatini muscle (LVPM); p — pterygoid process; pm — pterygoid muscle; s1,s2,s3 — subgroups of fibers of salpingopharyngeus muscle (SPM); t — tensor veli palatini muscle (TVPM); tp — tympanic bone process; tt — tendon of TVPM; arrow — posterior margin of palatal aponeurosis; co — constrictor muscles; cl — capitis longus muscle. A) Transitional area between tympanic and intermediate segments, showing beginning of ventral tubal extension. B-D) Different areas of intermediate segment, showing changes of shape of lumen, position of framing cartilage and bone, and paratubal muscles. E,F) Membranous nasopharyngeal segment.

flat and the rostral part is positioned more dorsally than the caudal part (Fig 2E,F). The size increases from 1.5 mm (mean 1.5, SD 0.09, n = 5) at the transition between the intermediate and the nasopharyngeal segments to 2.5 mm (mean 2.5, SD 0.11, n = 6) at the nasopharyngeal orifice. Dense fibrous tissue attaches the rostral part of the tube to the lamina medialis of the pterygoid process, a continuation of the rostral rim of the basisphenoid sulcus. The lamina medialis connects rostrally with the palatal bone and shows a short, caudally directed hamulus. The remaining part of this segment of the tube lacks any bony or cartilaginous framing (Fig 2E,F).

The anatomic position of the paratubal muscles and the main direction of the fibers are presented schematically in Figs 3 and 4.

Salpingopharyngeus Muscle. The SPM contains fibers that are inserted at different sites along the tube and run in diverse directions. Three subgroups, denominated as S1, S2, and S3, can be distinguished (Figs 3 and 4). Dorsally, a group of fibers (S1) arises from the caudal lamella of the C-shaped cartilage along nearly the whole length of the intermediate segment (Fig 3A). The fibers are attached to the ventral part of the cartilage by a tendon (Fig 5A) that contains both collagenous and elastic fibers (Fig 6A). The cartilage also shows the presence of numerous elastic fibers (Fig 6A). The muscle fibers course me-

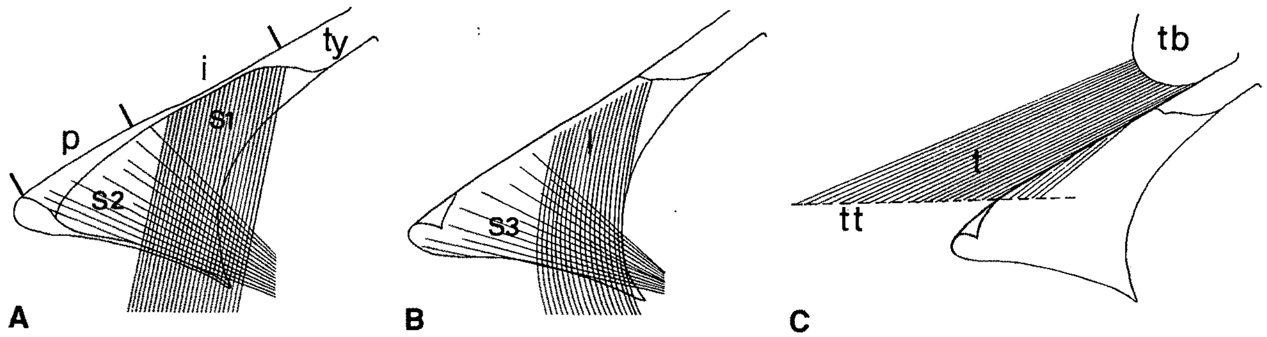


Fig 3. Diagrams of insertion and fiber direction of paratubal muscles. A) Dorsal wall with fibers of SPM (s1 and s2). i,p,ty — approximate positions of intermediate, pharyngeal, and tympanic segments, respectively. B) Ventral wall with fibers of LVPM (l) and SPM (s3). C) Direction of fibers of TVPM (t) attached to tympanic bone (tb) and to rostral wall and framing bone of tube. tt — tendon of TVPM.

dially, directed slightly rostrally (Fig 2E,F) in a nearly horizontal plane through the caudal gland, and are inserted into the raphe (dense connective tissue at the skull base) rostrally from the pharyngeal constrictor muscles and the capitis longus muscle (Fig 4).

A second group of fibers (S2) originates from the dorsal wall of the pharyngeal segment (Fig 3A). The majority of these fibers originate from the rostral part of the wall. The fibers course between the acini of the gland in a mediocaudal direction. Close to the nasopharyngeal orifice, the fibers converge and run caudad. They are inserted into the lateral pharyngeal wall ventrally from the constrictor muscles (Figs 2F and 4).

The fibers of the third group (S3) mainly originate from the rostral area of the ventral wall of the pharyngeal segment (Figs 2D-F, 3B, 4, and 7B,C). They run caudad for some distance and curve dorsally, at which point they are inserted into the lateral pharyngeal wall caudal to the S2 fibers (Fig 2F).

Staining for elastin revealed numerous elastic fibers in the lamina propria of the pharyngeal segment. They were also present between the muscle fibers of S2 and S3 muscles, especially of S3, and in their fibrous connections with the rostral part of the tube (Fig 6B).

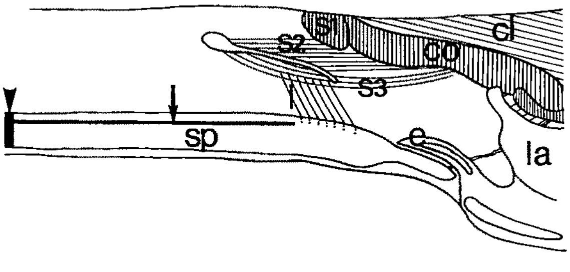


Fig 4. Schematic drawing of paramedial section of lateral wall of nasopharynx and adjacent structures. Shows position of orifice of eustachian tube and course of related paratubal muscles. cl — capitis longus muscle; co — constrictor muscles; e — epiglottis; l — LVPM; la — larynx; s1,s2,s3 — SPM; sp — soft palate; arrowhead — hard palate; arrow — palatal aponeurosis.

Tensor Veli Palatini Muscle. The TVPM is a fan-shaped muscle that is situated rostrally from the ET (Fig 3C). Two groups of fibers can be distinguished. The first group, which has no direct contact with the ET, constitutes the major part of the fibers. They are inserted into the rostromedial aspect of the tympanic process of the bulla, into the adjacent part of the dura of the petrotympanic fissure, and along the entire rostral aspect of the basisphenoid sulcus and the rostral aspect of the pterygoid process (Figs 2A-E and 5B). Ventrally from these mainly bone-anchored fibers, a second group is inserted into the fibrous tissue at the tip of the rostral lamella of the C-shaped cartilage and the rostral membranous wall of the intermediate segment of the tube (Figs 2B-D, 5C, and 7A,B). The fibers are inserted into a thick layer of connective tissue by tendinous structures (Fig 7D). In the membranous nasopharyngeal segment of the tube, in which the rostral part of the tube is connected to the pterygoid process, no muscle fibers are attached to the tube (Fig 2E).

All the fibers of the TVPM fan out in a rostromedial direction and end in a tendon just dorsolateral to the free edge of the lamina medialis of the pterygoid process (Figs 2D,E and 5B,C). The bone-anchored fibers are connected to the rostral part of the tendon, while the fibers associated with the ET are connected to the caudal part. The tendon bends at right angles around the bursa of the pterygoid process and continues as the palatal aponeurosis, just below the dorsal epithelium of the soft palate (Fig 5B,C).

The palatal aponeurosis, which has branches in the glandular tissue, is attached rostrally to the posterior edge of the palatal bone, and ends caudally at the site in which the fibers of the LVPM enter the palate (Fig 4).

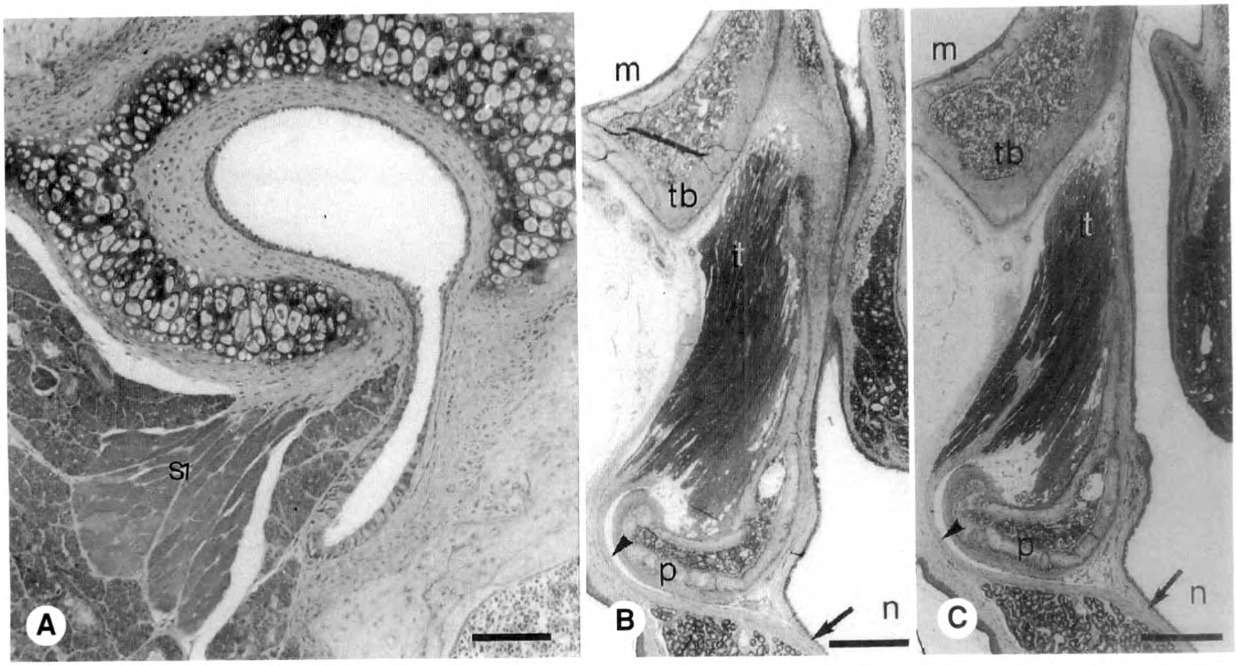


Fig 5. Toluidine blue. A) Coronal section of lateral part of intermediate segment of eustachian tube, showing attachment of SPM (s1) at posterior lamella of cartilage. Bar — 100 μm. B,C) Dorsoventral sections along longitudinal axis of rostral part of tube. Bars — 500 μm; m — middle ear; n — nasopharynx; arrowhead — tendon of TVPM rounding pterygoid process and passing into palatal aponeurosis (arrow). B) Attachment of fibers of TVPM (t) to tympanic bone (tb) and to framing bone of basisphenoid and pterygoid process (p). C) Slightly caudal from B, showing attachment to rostral membranous wall and pterygoid process (p).

Tensor Tympani Muscle. The tensor tympani muscle (TTM) is situated in a groove in the petrosal bone rostrally from the promontory and is connected to the medial process of the malleus by a tendon. It extends mediad in the sutura between the tympanic and the petrosal bones and is inserted into the meningeal tissue dorsally from the tympanic orifice of the ET. Histologically, no muscular or tendinous continuity between the TTM and TVPM was found.

Levator Veli Palatini Muscle. The LVPM is inserted by means of a tendon into the ventral tip of the rostral lamella of the C-shaped cartilage in the lateral part of the intermediate segment (Fig 3B). The tendon contains both collagenous and elastic fibers (Fig 6C).

The LVPM runs in a medial, slightly caudal direction along the ventral wall of the tube (Figs 2 and 3B). The attachment of the LVPM to the ventral wall of the tube coincides with the disappearance of the tympanic process in this area (Fig 2C). Close to the transition of the intermediate cartilaginous segment of the tube into the pharyngeal segment, the LVPM is attached along the entire ventral wall (Fig 2C). In contrast with the TVPM, the LVPM is separated from the epithelium by a very thin layer of connective tissue (Fig 7E), while there is thick perimysium between the LVPM and the TVPM (Figs 6C and 7A,B). At the transition into the membranous pharyngeal part, the LVPM becomes separated from the mucosa by muscle fibers of the S3 muscle (Figs 2D-F and 7B,C). Ventrally, the LVPM becomes bordered by fibers of the pterygoid muscle that originate from the caudal side of the pterygoid process and pterygoid hamulus (Figs 2E and 8). These fibers run posteriorly and blend with the S3 fibers; they are inserted into the lateral pharyngeal wall.

The LVPM runs in a mediocaudal direction dorsally from the caudal part of the pterygoid hamulus. It is inserted underneath the epithelium in the caudal part of the soft palate, caudal from the palatal aponeurosis (Figs 2F, 4, and 8). Fibers from both sides showed slight interdigitation.

DISCUSSION

The present study demonstrates that the rat ET is a very intricate structure. Throughout its length there is considerable variation in the shape of the tube and its relationship with the paratubal structures. The lumen of the tympanic part is permanently open. This segment of the tube can be compared to the bony part of the tube in the human.

The main part of the lumen in the intermediate and membranous pharyngeal segments is closed in the absence of muscular activity. Only the lateral part of the dorsal lumen in the intermediate segment and the rostral lumen near the nasopharyngeal orifice are permanently open.

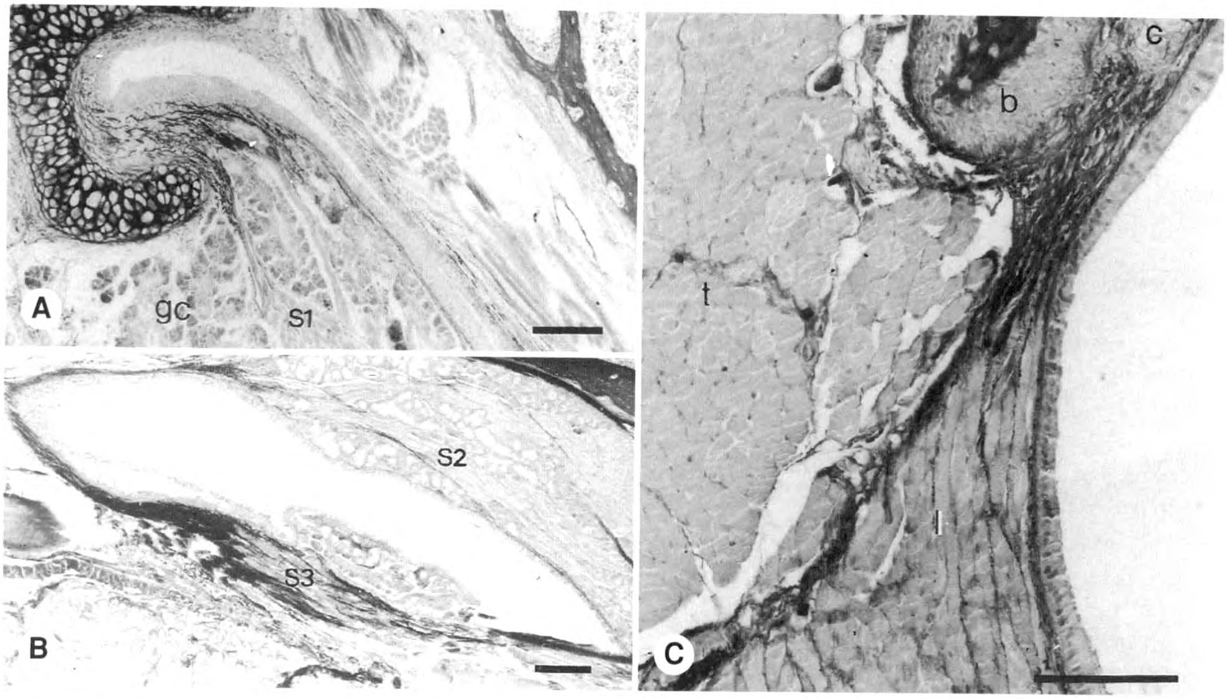


Fig 6. Sections from different sites of tube stained A,B) for elastin and C) for elastin and collagen. A) Coronal section of lateral part of intermediate segment of eustachian tube, showing numerous elastic fibers in tendinous insertion of SPM (s1) into caudal lamella of cartilage. gc — caudal gland; bar — 100 µm. B) Sagittal section through nasopharyngeal segment at orifice, showing elastic fibers between muscle fibers of SPM (s2 and s3) and in their tendinous connection with rostral part of tube. Bar — 200 µm. C) Coronal section showing fibrous attachment of LVPM (l) to anterior lamella of C-shaped cartilage (c) and framing basisphenoid bone (b). t — TVPM; bar — 100 µm.

The intermediate and pharyngeal segments together can be considered as analogous to the cartilaginous tube in the human, although in humans the paratubal cartilage is much more profuse and extends up to the nasopharyngeal orifice. These segments in the rat show a complex pattern of muscle fiber attachment from the SPM, TVPM, and LVPM.

The SPM is the most complicated muscle, with 3 groups of fibers that are attached either to the intermediate cartilaginous segment or to the membranous pharyngeal segment. Contraction of the (S1) fibers, which are attached to the tip of the caudal lamella of the C-shaped cartilage, moves the caudal wall by a hinge action in a medial direction, resulting in widening of the dorsal part of the lumen. Due to the elastic properties of the cartilage and the elastic fibers in the tendon of the muscle, this part of the tube returns to its original position when the muscle relaxes. The presence of this muscle is quite unique, because it appears to be the only paratubal muscle that functions independently of movements of the soft palate or pharyngeal wall. To our knowledge, the presence of a dilator muscle on the caudal side of the ET has not been described in other mammalian species.

Contraction of the S2 and S3 fibers, which are attached to the dorsal and ventral walls of the membranous part of the tube and are inserted into the dorsolateral pharyngeal wall, results in dilation of this part of the tube. The abundant elastic fibers close the tube after muscle relaxation. The presence of the SPM has also been reported by House[18] and Albiin et al,[17] but their data on the fiber distribution are controversial.

This situation in the rat differs from that in the human. In the human, the SPM is only a small muscle with a variable extent.[3,4,23] It originates in the inferior portion of the medial cartilaginous lamina. A proportion of these fibers are inserted into the lateral pharyngeal wall. This muscle has only been ascribed a minor role or no role at all in assisting with widening of the tubal orifice.[3,23] Probably, the difference from the rat tube is related to the fact that in humans the pharyngeal part of the tube is supported by cartilage.

In the rat, attachment of the TVPM and LVPM is confined to the intermediate part of the tube. The TVPM comprises a single anatomic belly, and all the fibers are connected to the palatal aponeurosis. However, there is functional compartmentalization. The majority of fibers that are attached to the paratubal bone only serve to tense the rostral soft palate. Fibers that are inserted close to the tip of the rostral lamella of the C-shaped cartilage cannot be effective in tubal dilation by rostral displacement of the

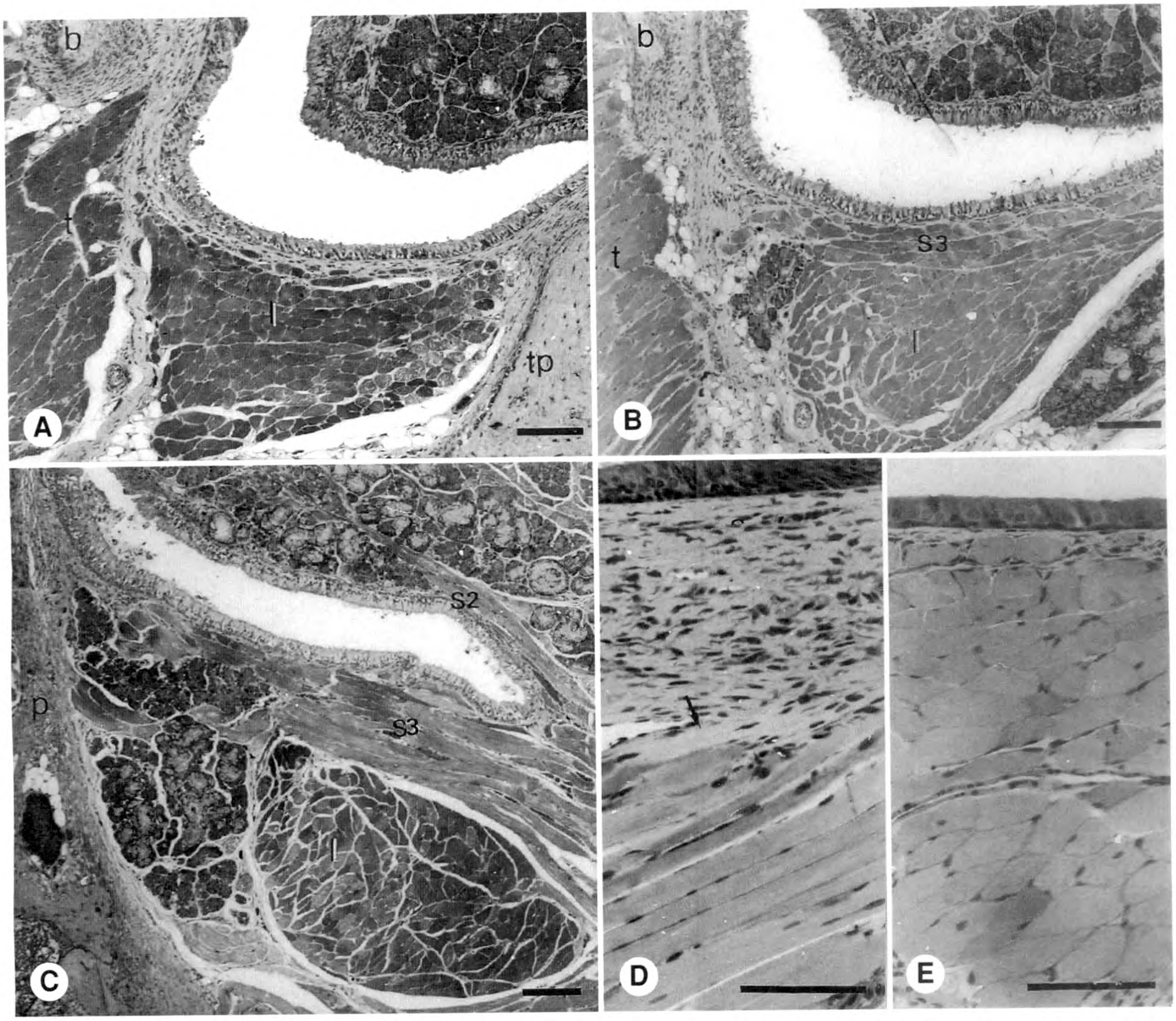


Fig 7. Toluidine blue. Bars — 100 µm. A-C) Details of sections shown in Fig 2C-E, demonstrating relationship of paratubal muscles to tube at different sites. b — basisphenoid bone; l — LVPM; p — pterygoid process; s2,s3 — SPM; t — TVPM; tp — tympanic bone process. Note difference in attachment of fibers of D) TVPM and E) LVPM shown at high magnification. Arrow — tendinous connection.

cartilage lamella, because this lamella is immobilized by its anchorage to the bone of the basisphenoid. Only the contraction of fibers that are directly inserted into the fibrous tissue of the membranous wall will be effective in pulling the wall in a rostroventral direction in conjunction with tensing of the soft palate.

The existence of 2 functional compartments has also been shown in the human,[2,5,6] the guinea pig,[19] and the rhesus monkey.[10,19] Although there is no unanimity on the mode of attachment or the site of insertion of the TVPM fibers in the human, it is generally believed that contraction causes displacement of the lateral cartilaginous lamina, which results in dilation of the lumen.[4,8]

The LVPM in the rat is attached directly to the ventral tubal wall in the intermediate segment. Its tendinous connection to the tip of the rostral lamella of the cartilage and its insertion into the caudal part of the soft palate suggest that muscle contraction will result in dorsal movement of the soft palate and elevation of the ventral wall of the tube, thus contributing to closure of the tube and its protective function. In addition, contraction of the LVPM might stabilize the ventral wall when the TVPM pulls the rostral wall in a rostroventral direction.

In the human, the LVPM has about the same anatomic position as in the rat; the fibers are arranged in the same direction, but there is no unanimity about their attachment to the tube or about the muscle's role in tubal function.[2,4,7,10,23] The LVPM has been proposed to assist in tubal dilation by elevating the soft palate and raising the floor of the tube,[9,13,23] but according to others, it may narrow the lumen or play a role in anchoring the posterior and middle parts of the inferolateral portion of the tube.[2,7,19]

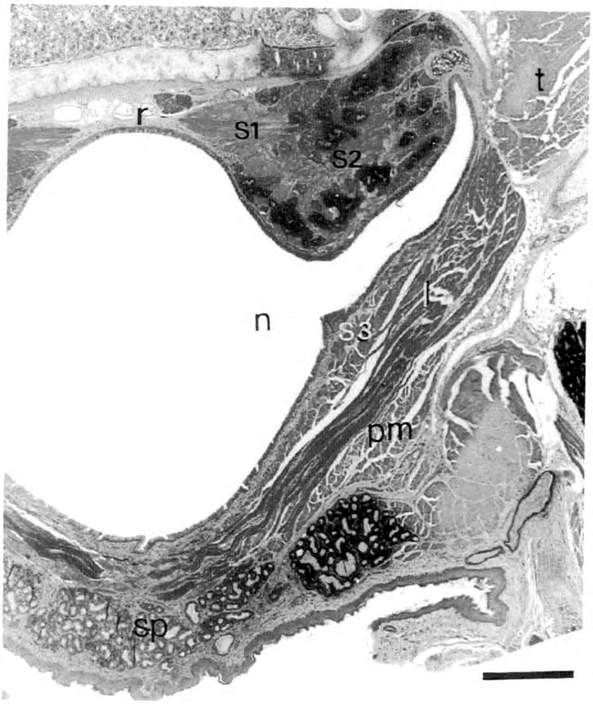


Fig 8. Coronal section showing relationship of LVPM (l) to eustachian tube and its insertion in posterior part of soft palate (sp; toluidine blue). Bar — 500 μm; n — nasopharynx; pm — pterygoid muscle; r — raphe; s1,s2,s3 — SPM; t — TVPM.

Our present observations show that the muscles of the tube are attached in a peculiar distribution pattern that appears to be related to the different features of the epithelial lining observed in a previous study.[20] In that study, we established that the dorsorostral portion was nearly completely lined by squamous epithelium, while the epithelial lining of the ventrocaudal portion consisted of ciliated-secretory epithelium. On the basis of these observations, spatial separation was postulated between the different functions of the tube.[20] The dorsal portion was suggested to serve ventilation, while the features of the remaining part were assumed to constitute a mucociliary clearance system. The exclusive attachment of the dilating muscles, SPM and TVPM, to the dorsal part of the tube strongly supports this assumption. Sando et al[24] have proposed a similar hypothesis, based on the predominance of squamous epithelium in the roof portion of the tube in humans and the site of insertion of the TVPM.

The ventrocaudal part of the cartilaginous tube in the rat only shows the attachment of fibers of the LVPM, which cannot assist in dilation of the lumen. It remains to be seen whether contraction of this muscle facilitates clearance.

ACKNOWLEDGMENT — The authors acknowledge the technical assistance of Els Camps.

REFERENCES

1. Bluestone CD, Paradise JL, Beery QC. Physiology of the eustachian tube in the pathogenesis and management of middle ear effusions. Laryngoscope 1972;82:1654-70.

2. Proctor B. Anatomy of the eustachian tube. Arch Otolaryngol 1973;97:2-8.

3. Rich AR. A physiological study of the eustachian tube and its related muscles. Bull Johns Hopkins Hosp 1920;31:206-14.

4. Graves G, Edwards L. The eustachian tube, review of its descriptive, microscopic, topographic and clinical anatomy. Arch Otolaryngol 1944;41:359-97.

5. Swarts JD, Rood SR. The morphometry and three-dimensional structure of the adult eustachian tube: implications for function. Cleft Palate Craniofac J 1990;27:374-81.

6. Rood SR, Doyle WJ. Morphology of tensor veli palatini, tensor tympani, and dilatator tubae muscles. Ann Otol Rhinol Laryngol 1978;87:202-10.

7. Seif S, Dellon AL. Anatomic relationships between the human levator and tensor veli palatini and the eustachian tube. Cleft Palate Craniofac J 1978;15:329-36.

8. Matsune S, Sando I, Takahashi H. Insertion of the tensor veli palatini muscle into the eustachian tube cartilage in cleft palate cases. Ann Otol Rhinol Laryngol 1991;100:439-46.

9. Honjo I, Okazaki N, Kumazawa T. Experimental study of the eustachian tube function with regard to its related muscles. Acta Otolaryngol (Stockh) 1979;87:84-90.

10. Doyle WJ, Rood SR. Comparison of the anatomy of the eustachian tube in the rhesus monkey (*Macaca mulatta*) and man. Implications for physiologic modeling. Ann Otol Rhinol Laryngol 1980;89:49-57.

11. Dickson DR. Anatomy of the normal velopharyngeal mechanism. Clin Plast Surg 1975;2:235-47.

12. Spauwen HM, Hillen B, Lommen E, Otten E. Three dimensional computer reconstruction of the eustachian tube and paratubal muscles. Cleft Palate Craniofac J 1991;28:217-20.

13. Eden AR, Laitman JT, Gannon PJ. Mechanisms of middle ear aeration: anatomic and physiologic evidence in primates. Laryngoscope 1990;100:67-75.

14. Simkins CS. Functional anatomy of the eustachian tube. Arch Otolaryngol 1943;38:476-84.

15. Doyle WJ, Casselbrant ML, Swarts JD, Bluestone CD. Observations on a role for the tensor veli palatini muscle in intrinsic palatal function. Cleft Palate Craniofac J 1990;27:317-20.

16. Cantekin EI, Doyle WJ, Bluestone CD. Effect of levator veli palatini excision on eustachian tube function. Arch Otolaryngol 1983;109:281-4.

17. Albiin N, Hellström S, Salén B, Stenfors LE, Söderberg O. The anatomy of the eustachian tube in the rat. Anat Rec 1983;207:513-21.

18. House EL. A myology of the pharyngeal region of the albino rat. Anat Rec 1953;116:363-78.

19. Gannon PJ, Eden AR, Laitman JT. Functional compartments of the tensor veli palatini muscle. Arch Otolaryngol Head Neck Surg 1994;120:1382-9.

20. Mulder JJS, Kuijpers W. The mucosal lining of the eusta-

chian tube of the rat. Acta Otolaryngol (Stockh) 1991;111:342-8.

21. van der Beek JMH, Kuijpers W. The mucoperiosteum of the middle ear in experimentally induced otitis media. Acta Otolaryngol Suppl (Stockh) 1984(suppl 414):71-7.

22. Hellström S, Salén B, Stenfors L-E, Söderberg O. Appearance of effusion material in the attic space correlated to an impaired eustachian tube function. Int J Pediatr Otorhinolaryngol 1983;6:127-34.

23. McMyn JK. The anatomy of the salpingo-pharyngeus muscle. J Laryngol Otol 1940;55:172-86.

24. Sando I, Takahashi H, Matsune S, Aoki H. Localization of function in the eustachian tube: a hypothesis. Ann Otol Rhinol Laryngol 1994;103:311-4.

≈

INTERNATIONAL MEETING ON OTOLOGY

The International Meeting on Otology of the Jean Causse Ear Clinic will be held June 5, 1999, in Béziers, France. For more information, please contact Robert Vincent, MD, Jean Causse Ear Clinic, Traverse de Béziers, 34440 Colombiers, France; telephone (33) 4-67-35-62-62; fax (33) 4-67-35-62-00.

Ann Otol Rhinol Laryngol 108:1999

EFFECT OF THYROPLASTY ON LARYNGEAL AIRFLOW

JANICE D. JANAS, MD
ERIK R. SWENSON, MD
PAT WAUGH, MS
ALLEN HILLEL, MD
SEATTLE, WASHINGTON

Thyroplasty has virtually replaced Teflon injection as the procedure of choice for treatment of the unilateral paralyzed vocal cord. Previous studies have shown that Teflon injection, by stiffening the vocal cord, decreases the extrathoracic airway obstruction occasionally measured by pulmonary function testing in patients with unilateral vocal cord paralysis. We became interested in the effect of thyroplasty on extrathoracic airflow. In this prospective study, patients underwent prethyroplasty and postthyroplasty pulmonary function testing. Flow volume loops combined with traditional spirometry were used. Postoperative pulmonary function tests were performed at least 2 months after surgery to allow resolution of surgical edema. Our study results support the previous finding that vocal cord paralysis alone causes some degree of extrathoracic obstruction. However, in contrast to Teflon injection, thyroplasty decreased extrathoracic airflow in all but 1 patient, and by criteria based on the ratio of the midexpiratory flow to the midinspiratory flow, caused new postoperative extrathoracic obstruction in 27% of patients. Symptomatic evidence of this obstruction may be more evident in those active patients with more ventilatory demand.

KEY WORDS — extrathoracic obstruction, flow volume loops, thyroplasty, vocal cord medialization.

INTRODUCTION

Laryngeal framework surgery, or thyroplasty, has virtually replaced Teflon injection as the procedure of choice for treatment of the paralyzed vocal cord. The procedures for the external manipulation of the laryngeal framework, popularized by Isshiki et al,[1,2] are in widespread use throughout the United States. The popularity of these procedures has been attributed to several significant advantages over Teflon injection. First, the procedure can be performed under local anesthesia and is well tolerated.[3] Next, the surgeon can adjust the degree of medialization on the basis of intraoperative phonation,[3] and the mucosal wave is preserved.[4] Finally, the procedure is infinitely adjustable and reversible.[4]

Several series have been published regarding the results and complications of thyroplasty.[4,5] Only perioperative complications, including airway edema with or without hematoma, and late complications of prosthesis migration have been shown.

In this procedure, the glottic airway is altered. The potential exists to narrow the glottic airway up to 50% of maximal abduction. Hence, we became interested in whether medialization of the vocal cord would lead to subjective or objective evidence of extrathoracic airflow obstruction in these patients.

Though no previous work has examined this question in regard to thyroplasty, Kashima[6] presented data from 43 patients with unilateral vocal cord paralysis who underwent Teflon vocal cord medialization. In his study, patients underwent preoperative and postoperative pulmonary function testing, including flow volume loops. He reported that a unilateral vocal cord paralysis alone reduced inspiratory flow rates in at least 50% of patients, and that Teflon injection, contrary to expectation, actually improved laryngeal airflow.

We devised a prospective study testing the pulmonary function of patients with unilateral vocal cord paralysis who were planning to undergo vocal cord medialization. Patients underwent preoperative and postoperative pulmonary function testing, including traditional spirometry and flow volume loops, to determine the effect of thyroplasty on laryngeal airflow. In addition, symptomatology, type of surgical procedure, voice quality, and degree of glottic closure on stroboscopic examination were analyzed.

METHODS

Twenty-three patients with unilateral vocal cord paralysis served as the patient population. Of these, 15 patients completed both the preoperative and postoperative evaluations.

Preoperatively, all patients were evaluated by both

From the Departments of Otolaryngology–Head and Neck Surgery (Janas, Hillel), Rehabilitation Medicine (Waugh, Hillel), and Medicine (Swenson), University of Washington, and the Departments of Medicine (Swenson) and Surgery (Hillel), Seattle Veterans Administration Medical Center, Seattle, Washington.

Presented at the meeting of the American Laryngological Association, Orlando, Florida, May 4-5, 1996.

CORRESPONDENCE — Allen Hillel, MD, University of Washington, Dept of Otolaryngology–Head and Neck Surgery, Box 356515, Seattle, WA 98195.

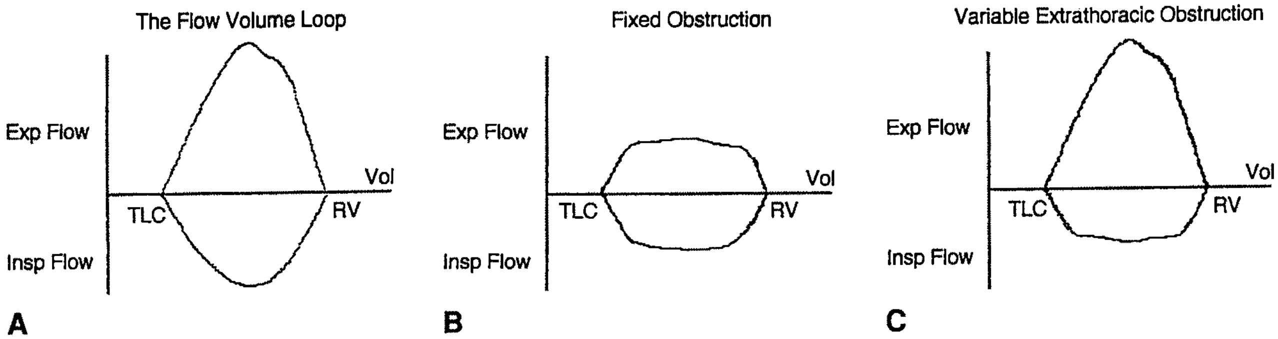


Fig 1. Obstructive patterns in flow volume loops. A) Typical normal loop. B) With fixed obstruction. C) With variable extrathoracic obstruction.

the senior laryngologist (A.H.) and the speech pathologist (P.W.). In addition to complete head and neck examination, all patients underwent videostroboscopy.

Each patient had pulmonary function tests, including routine spirometry and flow volume loops, performed at the Pulmonary Diagnostic Center of the University of Washington. The use of flow volume loops to evaluate large airway obstruction is well documented.[7-9] The indices of airflow measured (see below) and the flow volume loops were analyzed by a member of the pulmonary medicine department independent of the study protocol (E.R.S.).

In a flow volume loop, the subject inhales to total lung capacity, then does a maximal exhalation. Upon reaching the residual volume, he or she then inhales as quickly as possible back to total lung capacity (Fig 1A).

Extrathoracic obstruction of 2 types, fixed and variable, can be demonstrated on a flow volume loop. With a fixed obstruction, the airway diameter at the site of the lesion does not change with inspiration or expiration. Flow is limited by the obstruction, and thus, a plateau will be seen on both the inspiratory and expiratory curves (Fig 1B).

When the obstruction changes with the respiratory cycle, it is called a variable obstruction. Obstruction at the laryngeal level commonly affects the inspiratory portion of the flow volume loop more than the expiratory portion (Fig 1C). During forced inspiration, the pressure within the trachea is markedly negative compared to the atmospheric pressure. This transmural pressure decreases the diameter of the airway and thereby increases the obstruction. On expiration, positive transmural pressure within the trachea alleviates the obstruction. Thus, for an obstruction at the laryngeal level, the relative increase in obstruction seen on inspiration causes a plateau on the inspiratory portion of the flow volume loop, while the expiratory portion may or may not be affected.

Several measures of both inspiratory and expiratory airflow were used to determine whether evidence of laryngeal obstruction was present. Peak inspiratory flow (PIF) and forced inspiratory flow at 50% of vital capacity (FIF50%) were used as inspiratory measures. Peak expiratory flow (PEF), forced expiratory flow at 50% of vital capacity (FEF50%), and forced expiratory volume in 1 second (FEV1) were used as expiratory measures.

Finally, a ratio of expiratory to inspiratory flow rates was used as a marker for the presence of extrathoracic obstruction. At 50% of vital capacity, the ratio of the expired flow rate to the inspired flow rate (FEF50%/FIF50%) in normal subjects is 0.9 ± 0.3 (standard deviation).[10] In situations of laryngeal obstruction, the inspiratory flow, as discussed earlier, is often selectively reduced. Thus, as the denominator of this ratio decreases, the value of the ratio is increased. We chose a value of >1.3 to represent laryngeal obstruction, as Rotman et al[10] found that this value lies above the upper 1 standard deviation bound for both normal subjects and patients with chronic obstructive pulmonary disease. The preoperative means and postoperative means for all the airflow measures examined were compared with a 2-tailed paired *t*-test, and the p values were obtained.

All surgery was performed by the senior laryngologist. The speech pathologist was present for each procedure. Local anesthesia with intravenous sedation was used in all cases. The patient was positioned supine with a shoulder roll for neck extension. A nasopharyngoscope was positioned for continuous visualization of the glottis throughout the procedure. An incision was made in a horizontal skin crease above the thyroid cartilage. Superior and inferior flaps were elevated and the strap muscles lateralized to expose the thyroid cartilage. On the side of the immobile cord, a 4 × 8-mm window was made at the level of the true vocal cord. A silicone offset ramp prosthesis[11] was then fashioned and placed. The patient was asked to vocalize, and the prosthesis was modified as appropriate to maximize the voice re-

TABLE 1. SUMMARY OF DATA

Patient	*Age*	*Sex*	*Voice Postop*	*Symptoms Postop*	*Surgery*	*Ratio Preop*	*Ratio Postop*
1	45	F	Good	No	M	0.13	0.06
2	78	M	Good	No	M/CTp	0.26	0.59
3	67	F	Good	No	bM	0.56	0.59
4	81	M	Poor	No	M/CTp	0.58	0.45
5	45	M	Excellent	Yes	M	0.59	1.35
6	64	F	Excellent	Yes	M/CTp	0.63	0.80
7	48	M	Good	Yes	M/CTp	0.83	1.24
8	70	M	Excellent	No	M	0.86	0.94
9	70	F	Good	No	M/CTp	0.95	2.18
10	44	M	Excellent	No	M/CTp/AA	0.96	0.86
11	63	M	Good	No	M	1.16	1.35
12	46	F	Excellent	Yes	M/CTp/AA	1.23	2.33
13	72	F	Excellent	No	M/CTp	1.35	1.47
14	35	F	Good	No	M	1.44	1.64
15	25	M	Good	No	M	2.39	3.14

Ratio — FEF50%/FIF50% (see text), M — medialization, CTp — cricothyropexy, bM — bilateral medialization, AA — arytenoid adduction.

sult. All patients had at least a unilateral medialization (Table 1). One of the patients with a bilateral vocal cord weakness had bilateral silicone implants. In several cases, a cricothyropexy was additionally performed. Two patients also underwent arytenoid adduction in addition to silicone implant medialization. The wound was then closed over a Penrose drain, and a pressure dressing was placed. All patients were admitted overnight for observation and discharged the following morning.

Postoperatively, patients were judged for voice improvement on a 4-station scale. Excellent voice corresponded to excellent pitch and volume. Good voice meant improvement from preoperative status but with some residual deficits in volume or persistent breathiness. Fair corresponded to improved but still markedly abnormal. Poor indicated no voice improvement. In addition, all patients underwent postoperative videostroboscopy. The criterion for stroboscopic medialization was closure of the glottic gap with phonation. Postoperative pulmonary function tests were performed at least 2 months after surgery to allow resolution of surgical edema.

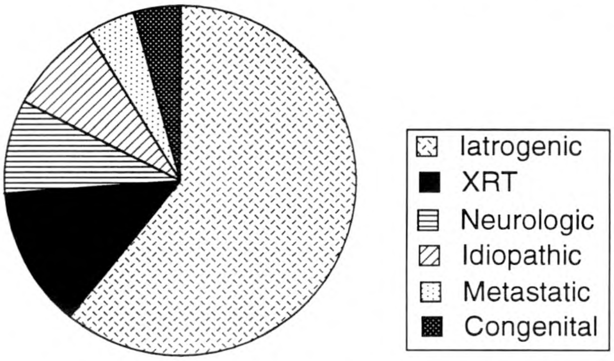


Fig 2. Causes of vocal cord paralysis. Iatrogenic category accounted for over half of vocal cord paralyses seen. XRT — radiotherapy.

RESULTS

Unilateral Vocal Cord Paralysis. The subjects included 14 men and 9 women with a mean age of 54 years. The majority of patients had sustained a vocal cord paralysis during a surgical procedure. The causes of the vocal cord paralyses in all patients are shown in Fig 2. The right vocal cord was paralyzed in 9 patients, the left in 12 patients. Two patients had underlying neurologic deficits that resulted in an incomplete paralysis of both vocal cords.

None of the patients in this series had a subjective complaint of laryngeal airflow obstruction, such as dyspnea or stridor, as a result of unilateral vocal cord paralysis alone. By the criterion of Rotman et al[10] — FEF50%/FIF50% greater than 1.3 — 4 patients (17%) showed evidence of laryngeal obstruction as a result of unilateral vocal cord paralysis alone.

Effect of Thyroplasty on Laryngeal Airflow. Fifteen patients completed both the preoperative and postoperative evaluations, including complete pulmonary function testing. Table 2 shows the mean and standard deviation of all flow measures used in both the preoperative and postoperative tests. The FEV_1 was not changed as a result of thyroplasty. Both measures of expiratory flow — PEF and FEF50% — were decreased across the group postoperatively as compared to preoperatively, but the difference was not significant. Both measures of inspiratory flow — PIF and FIF50% — were decreased in 14 of the 15 patients. The differences in both these measures

TABLE 2. AIRFLOW MEASURES

	FEV1	*PIF*	*FIF50%*	*PEF*	*FEF50%*	*Ratio*
Preop (mean ± SD)	2.84 ± 1.09	4.16 ± 1.51	3.96 ± 1.46	6.17 ± 2.77	3.63 ± 1.59	0.93 ± 0.55
Postop (mean ± SD)	2.74 ± 1.15	3.35 ± 1.53	3.08 ± 1.44	5.85 ± 2.82	3.39 ± 1.84	1.26 ± 0.81
Change	−0.10	−0.81	−0.88	−0.32	−0.24	0.33
p	.12	.0001*	.0007*	.14	.94	.0093*

Ratio — FEF50%/FIF50%. (See text for explanation of measures.)

*Significant.

across the group were significant (p = .0001 and p = .0007, respectively). The FEF50%/FIF50% increased in 12 of the 15 patients, and this difference between the preoperative and postoperative test results was significant (p = .0093).

Laryngeal Obstruction on Flow Volume Loops. The FEF50%/FIF50% values for the 15 patients who completed preoperative and postoperative testing are shown in Table 1. Three patients (No. 13, unilateral medialization with cricothyropexy; No. 14, unilateral medialization; and No. 15, unilateral medialization) had preoperative ratios of greater than 1.3. All of these patients showed an increase in this ratio after thyroplasty. Four patients (No. 5, unilateral medialization; No. 9, unilateral medialization with cricothyropexy; No. 11, unilateral medialization; and No. 12, unilateral medialization with arytenoid adduction and cricothyropexy) had FEF50%/FIF50% ratios that were increased to above 1.3 postoperatively. Patient 12 (age 46) was symptomatic postoperatively, with stridor on exertion. Patient 12's flow volume loop showed flattening of both the expiratory and inspiratory portions, compatible with a fixed extrathoracic obstruction (Fig 3). Patient 5 (age 45) was symptomatic, with stridor in cold weather and on exertion. Thus, 27% of the patients in this series had evidence of new postoperative obstruction on their flow volume loops.

Symptoms of Laryngeal Obstruction. The FEF50%/FIF50% did not seem to predict those patients with symptoms of airflow obstruction. Table 1 reveals that 7 patients had ratios compatible with airflow obstruction postoperatively. Of these, patients 5 and 12, previously discussed, were the only 2 symptomatic. Two patients (Nos. 14 and 15) had sustained their vocal cord paralyses after craniotomies that resulted in neurologic deficits that limited their ability to perform exertional activity. The remaining 3 patients with a postoperative ratio of greater than 1.3 had a mean age of 68 years.

Figure 4A shows the presence of symptoms plotted against the postoperative FEF50%/FIF50%. The symptomatic patients could not be distinguished from

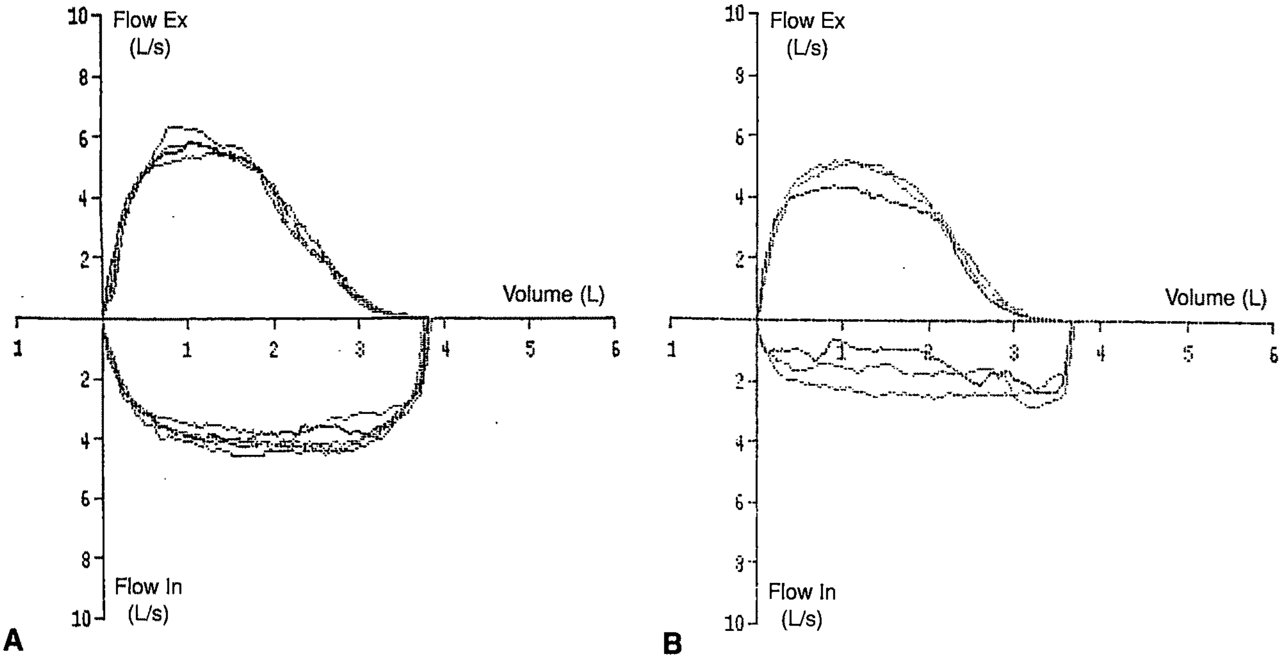


Fig 3. (Patient 12) A) Preoperative and B) postoperative flow volume loops. This patient was symptomatic, with stridor on exertion postoperatively. Note flattening of both inspiratory and expiratory portions of flow volume loops, compatible with fixed extrathoracic obstruction.

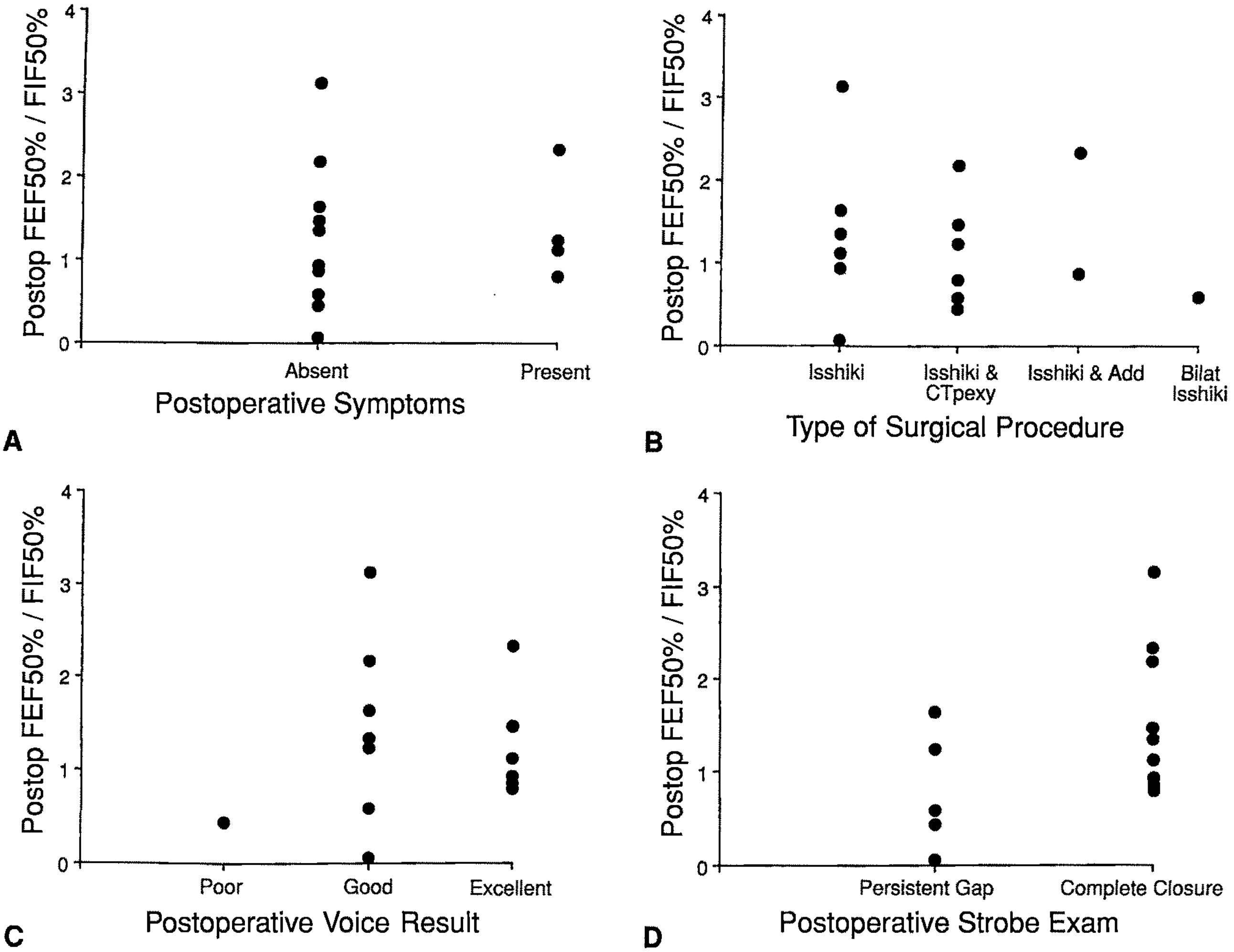


Fig 4. Postoperative FEF50%/FIF50% (see text) ratio versus other variables. A) Presence of symptoms versus postoperative FEF50%/FIF50%. Symptoms were not correlated to high FEF50%/FIF50% ratios. B) Type of surgical procedure performed versus postoperative FEF50%/FIF50%. Additional procedures of cricothyropexy (CTpexy), ipsilateral arytenoid adduction (Add), or bilateral silicone medialization (Bilat Isshiki) did not correlate with higher FEF50%/FIF50%. Isshiki — unilateral silicone implantation alone. C) Postoperative voice result versus postoperative FEF50%/FIF50%. Excellent voice result did not mandate higher FEF50%/FIF50%. D) Findings on postoperative stroboscopic examination versus FEF50%/FIF50%.

the asymptomatic patients on the basis of postoperative FEF50%/FIF50% (Fig 4A).

Of note, the 4 patients who were symptomatic had a mean age of 51 years. The subjective complaints of these patients were quite varied. The 2 patients (Nos. 5 and 12) whose postoperative flow volume loops were compatible with obstruction complained of stridor on exertion. Patient 6 was symptomatic, with dyspnea on exertion postoperatively. Patient 7 had a subjective complaint of airflow limitation with exertion, but stated that this sensation did not at all limit activity with exertion.

Type of Surgical Procedure. Although the sample sizes were small, the postoperative FEF50%/FIF50% was next evaluated in regard to the type of surgical procedure performed (Fig 4B). A higher FEF50%/FIF50% did not relate to the type of surgical procedure performed. Silicone medialization with or without cricothyropexy resulted in similar ratios. The 1 patient who underwent a bilateral silicone medialization had a low-range FEF50%/FIF50% postoperatively. Of the 2 patients who underwent arytenoid adduction, 1 did have a high postoperative FEF50%/FIF50%, but the other was 1 of the 3 patients whose ratios did not increase postoperatively.

Voice and Stroboscopic Results. The FEF50%/FIF50% was next examined in relation to the voice result (Fig 4C) and the postoperative stroboscopic examination (Fig 4D). Only 1 patient had essentially no change in voice, and this patient had a low postoperative FEF50%/FIF50%. For the patients who had either good or excellent voice results, there was no relationship to postoperative FEF50%/FIF50% (Fig 4C). Interestingly, the presence or absence of complete glottic closure did not correlate with the postoperative FEF50%/FIF50% (Fig 4D). Those with complete glottic closure had a slightly higher mean score, but the difference was not statistically significant.

DISCUSSION

Unilateral vocal cord paralysis did not produce symptoms of laryngeal obstruction in this patient population. However, 17% of patients did show subclinical evidence of obstruction on flow volume loops. In Kashima's[6] work, among 43 patients with unilateral vocal cord paralysis, 22% had symptoms of airway impairment and 58% had signs of airflow obstruction on pulmonary function tests. Kashima postulated that the flaccid vocal fold and ventricle were drawn medially by the force of laryngeal airflow, resulting in greater turbulence and limitation of airflow. Though our results confirm that a unilateral vocal cord paralysis can dampen laryngeal flow, we found this effect at one third the frequency that Kashima demonstrated.

The low incidence of laryngeal airflow obstruction preoperatively seen in this study is in part due to the criterion used for defining its presence. In this study, we used an FEF50%/FIF50% of 1.3. In Kashima's[6] work, the criterion for laryngeal obstruction was 1.15. Using Kashima's criterion in our study produces 7 of 23 patients (30%) with preoperative pulmonary function test evidence of laryngeal obstruction. Interestingly, this still is only half that shown by Kashima.

In Kashima's[6] work, 60% of patients showed *improvement* in laryngeal airflow after Teflon injection. Kashima postulated that because Teflon stiffened the cord, it was no longer drawn into the midline during high laryngeal flow rates, and thus, airflow was improved. In distinct contrast, no patients in our series showed resolution of their preoperative laryngeal obstruction after thyroplasty. Of the 3 patients with preoperative obstruction who completed postoperative evaluation, all showed persistent, increased obstruction postoperatively. In addition, 27% showed new obstruction after silicone medialization of the vocal cord. Of these, 2 young patients were symptomatic. Perhaps the fact that thyroplasty does not stiffen the vocal cord[4] is cause for the persistent obstruction. The degree of cord medialization in thyroplasty compared to Teflon injection may perhaps account for new postoperative laryngeal obstruction. The precise control of silicone implantation may allow the cord to be more fully medialized in thyroplasty than in Teflon injection. Interestingly, the voice result and final position of the vocal cord as determined by glottic closure on phonation did not appear to increase the relative impairment of airflow. An excellent voice result did not require a degree of medialization that necessitated airflow limitation.

We also examined whether additional procedures performed with silicone vocal cord medialization, namely, cricothyropexy and arytenoid adduction, had any effect on laryngeal airflow. Although the surgical numbers are small, patients who underwent these additional procedures did not have any greater decrease in their inspiratory airflows than those who underwent silicone medialization alone.

Symptoms of postoperative obstruction did not correlate to the pulmonary function test results. Only 2 patients — a 46-year-old woman and a 45-year-old man — showed changes in their FEF50%/FIF50% ratios compatible with obstruction and were symptomatic. Interestingly, those patients with pulmonary function tests suggestive of postoperative obstruction had a mean age of 68 years, whereas the symptomatic patients had a mean age of 52 years. This nearly 20-year age difference suggests that pulmonary function tests might not be sensitive enough to reveal subtle effects in laryngeal airflow that cause symptoms in an active person. Of note, none of the patients in this series who were symptomatic requested that the medialization procedure be reversed.

In conclusion, our study found that on the basis of pulmonary function tests, thyroplasty surgery worsened the FEF50%/FIF50% ratio in 12 of 15 patients and created new extrathoracic obstruction in 4 of 15 patients. Fortunately, symptomatic evidence of this obstruction is uncommon and may be more evident in those active patients with more ventilatory demand. A vocal cord paralysis alone may cause some signs of extrathoracic obstruction in about one fifth of patients. We feel that the possibility of laryngeal airflow limitation should be discussed with patients, especially younger or more active patients, as part of routine preoperative counseling for thyroplasty.

REFERENCES

1. Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. Acta Otolaryngol (Stockh) 1974;78:451-4.

2. Isshiki N, Okamura H, Ishikawa T. Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol (Stockh) 1975;80:465-73.

3. Koufman JA. Laryngoplasty for vocal cord medialization: an alternative to Teflon. Laryngoscope 1986;96:726-31.

4. Maves MD, McCabe BF, Gray S. Phonosurgery: indications and pitfalls. Ann Otol Rhinol Laryngol 1989;98:577-80.

5. Tucker HM, Wanamaker J, Trott M, Hicks D. Complications of laryngeal framework surgery (phonosurgery). Laryngoscope 1993;103:525-8.

6. Kashima HK. Documentation of upper airway obstruc-

tion in unilateral vocal cord paralysis: flow volume loop studies in 43 patients. Laryngoscope 1984;94:923-37.

7. Hyatt RE. Evaluation of major airway lesions using the flow-volume loop. Ann Otol Rhinol Laryngol 1975;84:635-42.

8. Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper central airways. Am J Med 1976;61:85-92.

9. Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow volume loops. Am Rev Respir Dis 1973;108:475-81.

10. Rotman HH, Liss HP, Weg JG. Diagnosis of upper airway obstruction by pulmonary function testing. Chest 1975;68:796-9.

11. Koufman JA, Isaacson G. Laryngoplastic phonosurgery. Otolaryngol Clin North Am 1991;24:1151-77.

≈

FUNCTIONAL ENDOSCOPIC SINUS SURGERY

Functional Endoscopic Sinus Surgery — Basic and Advanced Techniques will be held in Graz, Austria, in English (July 1-3, 1999) and in German (September 2-4, 1999). For more information, contact Claire Zwerina, Secretary to Prof Stammberger, ENT-Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43/316/385/3425.

Ann Otol Rhinol Laryngol 108:1999

IMMUNE RESPONSE TO *FUSOBACTERIUM NUCLEATUM* AND *PREVOTELLA INTERMEDIA* IN PATIENTS WITH CHRONIC MAXILLARY SINUSITIS

ITZHAK BROOK, MD, MSC PAULA YOCUM, MSC
WASHINGTON, DC

Our objective was to study the immune response to 2 anaerobic bacteria in patients with chronic maxillary sinusitis. Immunoglobulin G class antibody titers to *Fusobacterium nucleatum* and *Prevotella intermedia* were measured by enzyme-linked immunosorbent assay. Serum levels in the patients were determined on the day sinus aspiration for culture was done, and 75 to 90 days later, after completion of antimicrobial therapy, *Prevotella intermedia* was isolated from 16 aspirates, and *F nucleatum* from 12. Median antibody levels at day 1 for *F nucleatum* and *P intermedia* were significantly higher in patients whose serum aspirates harbored these organisms than at days 75 to 90 in those who were cured ($p < .05$). However, the levels stayed elevated in the 5 patients who did not improve. The elevated antibody levels to *F nucleatum* and *P intermedia*, known oral pathogens, suggest a potential pathogenic role for these organisms in chronic maxillary sinusitis.

KEY WORDS — antibodies, chronic sinusitis, *Fusobacterium nucleatum*, *Prevotella intermedia*.

INTRODUCTION

The bacterial causation of chronic sinusitis has been studied extensively,[1-4] and anaerobic bacteria were found to be the predominant isolates. These organisms include pigmented *Prevotella* and *Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus* species. However, even though anaerobic bacteria predominated in aspirates of chronic sinusitis and were shown to induce sinusitis in animal models,[5] their exact pathogenic role was controversial.[6]

The role of anaerobic bacteria in chronic sinusitis was investigated by measurement of the antibodies of the immunoglobulin G class to 2 organisms commonly recovered from sinus aspirates (*Fusobacterium nucleatum* and *Prevotella intermedia*). The presence of these antibodies was investigated by enzyme-linked immunosorbent assay (ELISA) in patients in the chronic and recovery stages of chronic sinusitis.

PATIENTS AND METHODS

The 23 patients (14 men) presented in this report were seen in the outpatient clinic for chronic maxillary sinusitis. Their ages ranged from 18 to 63 years (average 27 years). The course of the disease had to be at least 3 months in duration. Patients' complaints included facial pain, frontal headache, purulent nasal discharge, fever, and malaise. Inflammation of the maxillary sinuses was diagnosed after reviewing the clinical and radiologic findings. Occipitomental (Waters' view), lateral, oblique, and verticomental views and computed tomography (CT) scans were obtained. Sinusitis was defined radiographically as complete sinus opacity, an air-fluid level, or mucous membrane thickening of at least 6 mm in the maxillary sinus. For the Waters' view, mucosal thickening of the maxillary sinuses was measured as the shortest distance from the air-mucosal interface to the most lateral part of the maxillary sinus wall. In each instance, the antimicrobial therapy indicated was started after culture had been obtained.

Specimens were obtained through maxillary sinus antrostomies under local anesthesia, employing strict asepsis to avoid contamination. Aspirates were immediately transported to the laboratory in a corked syringe. The time between specimen collection and inoculation never exceeded 30 minutes. For aerobic organisms, the specimens were inoculated onto sheep blood, chocolate, and MacConkey's agar plates, incubated at 37°C in air (MacConkey's agar) or in air with carbon dioxide 5% (blood and chocolate agar), and examined after 24 and 48 hours. For anaerobes, the material was plated onto prereduced vitamin K_1–enriched *Brucella* blood agar, a blood agar plate containing kanamycin sulfate and vancomycin hydrochloride, and a blood agar plate containing colistin and nalidixic acid and inoculated into enriched thioglycolate broth.[7] The plates were incubated in anaerobic jars and examined after 48, 96, and 120 hours. The thioglycolate broth was incubated for 14 days. Aerobic and anaerobic bacteria were identified by previously described techniques.[7,8]

Two serum samples were obtained from each pa-

From the Department of Pediatrics, Georgetown University, Washington, DC.

CORRESPONDENCE — Itzhak Brook, MD, MSc, PO Box 70412, Chevy Chase, MD 20813-0412.

SERUM LEVELS FOR BACTERIA AS DETERMINED BY ELISA IN 23 PATIENTS WITH CHRONIC MAXILLARY SINUSITIS

	Fusobacterium nucleatum		Prevotella intermedia	
	Isolated (n = 12)	*Not Isolated (n = 11)*	*Isolated (n = 16)*	*Not Isolated (n = 7)*
Day 1	152.2 ± 16*	32.6 ± 6	167.5 ± 18*	38.7 ± 8
Days 75-90		25 ± 7		24.4 ± 6
Cured	58.3 ± 4 (n = 10)		63.0 ± 7 (n = 13)	
Failed	129 ± 3 (n = 2)		171 ± 9 (n = 3)	

Data are median ± SE.

ELISA — enzyme-linked immunosorbent assay.

*Median test $p < .05$ compared to cured patients and patients without bacteria isolated.

tient; the first was collected when the patient was first seen, and the second was taken 75 to 90 days later. The serum samples were stored at –70°C.

All the patients received antimicrobial therapy for 28 to 36 days. The antimicrobials included amoxicillin–clavulanate potassium (12 patients) and clindamycin phosphate (11). They also received decongestants for 3 to 5 days. They were followed in the outpatient clinic for at least 90 days.

Immunologic Methods. Antibody titers were measured by ELISA on 2 separate occasions by a modification of the method described by Ebersole et al.[9] The assay was run twice, in a single run on each occasion. Isolates of the following bacteria served as sources of antigens: *P intermedia* American Type Culture Collection (ATCC) strain 25611 and *F nucleatum* ATCC strain 25586. The processing of antigens and the ELISA test were performed as described previously.[10]

Statistical Analysis. The median test[11] was used to compare the data sets. For this purpose, the data were transformed to conform to the positive and negative control readings for each batch of 20 data values. The positive control reading was assigned an arbitrary value of 100 units, and the negative control reading a value of 0. Actual data values were then transformed as a straight line adjustment between these 2 values.

RESULTS

Microorganisms were isolated from all specimens. Eighty-seven isolates were recovered from the 23 patients (3.8 isolates per specimen); of these, 18 were aerobic or facultative (0.8 isolates per specimen), and 69 were anaerobic (3.0 isolates per specimen). Anaerobic bacteria were found in 11 (48%) instances, aerobic bacteria only in 2 (9%), and mixed aerobic and anaerobic bacteria in 10 (43%) cases. Mixed flora were present in all specimens, and the number of isolates varied from 2 to 6 per specimen. Some of the microbiologic data were previously published.[12]

The predominant isolates were *Prevotella* spp (24 isolates, including 16 *P intermedia*), *Fusobacterium* spp (14 isolates, including 12 *F nucleatum*), and *Peptostreptococcus* spp (13 isolates). Eighteen (78%) of the patients resolved their infection within 90 days of follow-up.

The infection persisted in 5 patients, 3 of whom received amoxicillin-clavulanate, and 2 of whom received clindamycin. Sinus aspirates were performed in these patients. *Fusobacterium nucleatum* was recovered in 2 of these patients in the aspirates obtained at day 1 and at the second culture (days 71 and 82), and *P intermedia* was isolated in 3 patients from the first aspirate and from 2 in the second culture (days 68 and 70). The patients received further therapy with antimicrobials. Three patients cleared their infection after additional therapy for 4 to 6 weeks, and 2 had persistent infection.

The median serum antibody levels at day 1 for *F nucleatum* and *P intermedia* were significantly higher (see Table) in patients whose sinus aspirates harbored these organisms than at days 75 to 90 in those who recovered from their infection ($p < .05$). These levels were also higher ($p < .05$) than those found in serum of patients who did not harbor these organisms, at day 1 and days 75 to 90. The antibody levels in those who failed to improve remained high at days 75 to 90. No follow-up serum levels were obtained from these patients.

DISCUSSION

This study confirms the findings of previous studies that illustrated the predominance of anaerobic bacteria in chronic maxillary sinusitis.[1-4] It also demonstrates for the first time elevated antibody titers to *F nucleatum* and *P intermedia* at the peak of the infection — the two most predominant anaerobes recovered in the infection. With the recovery of the patients, the antibody titers declined. However, the levels remained high in those who did not improve. As the antibody levels for other aerobic and anaerobic bacteria that were also recovered from the chronically infected sinuses were not investigated, it is possible that antibodies against other species may also be involved.

Fusobacterium nucleatum and *P intermedia* are known oral pathogens[13] and have been isolated as predominant species in several other chronic respiratory tract infections, which included aspiration pneumonia, lung abscesses, chronic otitis media, retropharyngeal and peritonsillar abscesses, and bacteremia associated with these infections.[13,14] Antibodies against *P intermedia* were found to be elevated compared to controls in patients with nonstreptococcal tonsillitis.[10]

Support for the importance of anaerobic bacteria in chronic sinusitis is the superior efficacy of antimicrobial therapy directed against these organisms, as compared to therapy with less effective agents.[15]

We have previously illustrated the transition that occurs in the microbiology of maxillary sinusitis as the infection gradually progresses from acute to chronic.[16] As chronic infection develops, the aerobic and facultative species are gradually replaced by strictly anaerobic bacteria. These changes may be due to the selective pressure of antimicrobial agents that enable resistant organisms to survive. Moreover, the effects of chronic infection may lead to the development of conditions appropriate for the growth of anaerobic bacteria. These changed conditions include a reduction in oxygen tension and an increase in acidity within the sinus cavity. These are caused by the persistent edema and swelling within the sinus cavity that reduces blood supply and the consumption of oxygen by the aerobic component of the sinus cavity bacterial flora.[17,18]

ACKNOWLEDGMENT — The authors acknowledge the editorial assistance of Sarah Blaisdell.

REFERENCES

1. Frederick J, Braude AI. Anaerobic infection of the paranasal sinuses. N Engl J Med 1974;290:135-7.
2. Evans FO, Sydnor JB, Moore WEC, et al. Sinusitis of the maxillary antrum. N Engl J Med 1975;293:735-9.
3. Carenfelt C, Lundberg C, Nord CE, Wretlind B. Bacteriology of maxillary sinusitis in relation to quality of the retained secretion. Acta Otolaryngol (Stockh) 1978;86:298-302.
4. Brook I. Bacteriological features of chronic sinusitis in children. JAMA 1981;246:967-9.
5. Westrin KM, Norlander T, Stierna P, Carlsöö B, Nord CE. Experimental maxillary sinusitis induced by *Bacteroides fragilis*: a bacteriological and histological study in rabbits. Acta Otolaryngol (Stockh) 1992;112:107-12.
6. Wald RE. Chronic sinusitis in children. J Pediatr 1995; 127:339-47.
7. Summanen P, Baron EJ, Citron DM, Strong CA, Wexler HM, Finegold SM. Wadsworth anaerobic bacteriology manual. 5th ed. Belmont, Calif: Star Publishing, 1995.
8. Murray PR, Baron EJ, Pfaller MA, Trenover PC, Yolken RH. Manual of clinical microbiology. 5th ed. Washington DC: American Society for Microbiology, 1993.
9. Ebersole JL, Frey DE, Taubman MA, Smith DJ. An ELISA for measuring serum antibodies to *Actinobacillus actinomycetemcomitans*. J Periodontal Res 1980;15:621-32.
10. Brook I, Foote PA Jr, Slots J, Jackson W. Immune response to *Prevotella intermedia* in patients with recurrent nonstreptococcal tonsillitis. Ann Otol Rhinol Laryngol 1993;102: 113-6.
11. Conover WJ. Pediatric non-parametric statistics. 2nd ed. New York, NY: John Wiley and Sons, 1980:171-8.
12. Brook I, Yocum P, Frazier EH. Bacteriology and beta-lactamase activity in acute and chronic maxillary sinusitis. Arch Otolaryngol Head Neck Surg 1996;122:418-28.
13. Brook I. Pediatric anaerobic infection: diagnosis and management. 2nd ed. St Louis, Mo: CV Mosby, 1989.
14. Brook I. Anaerobic bacteremia: 12-year experience in two military hospitals. J Infect Dis 1989;160:1071-5.
15. Brook I, Thompson DH, Frazier EH. Microbiology and management of chronic maxillary sinusitis. Arch Otolaryngol Head Neck Surg 1994;120:1317-20.
16. Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxillary sinusitis. J Med Microbiol 1996;45:372-5.
17. Aust R, Drettner B. The oxygen exchange through the mucosa of the maxillary sinus. Rhinology 1974;12:11-23.
18. Carenfelt C, Lundberg C. Purulent and non-purulent maxillary sinus secretions with respect to pO2, PCO2 and pH. Acta Otolaryngol (Stockh) 1977;84:138-44.

Ann Otol Rhinol Laryngol 108:1999

THE "SIGN OF THE RISING TIDE" DURING SWALLOWING FIBEROSCOPY: A SPECIFIC MANIFESTATION OF ZENKER'S DIVERTICULUM

SOPHIE PÉRIÉ, MD
HENRI-PIERRE DERNIS, MD
BRUNO ANGELARD, MD
GUY MONCEAUX, MD
JEAN LACAU ST GUILY, MD
PARIS, FRANCE

Pooling of secretions in the hypopharynx is a common sign of an impaired upper esophageal sphincter. Until now, no specific manifestation, observed by flexible laryngoscopy, of Zenker's diverticulum has been reported. Direct visualization of the diverticulum can be missed during flexible laryngoscopic examination. In this series of 12 patients with hypopharyngeal diverticulum, we have described a manifestation of Zenker's diverticulum obtained on videofiberoscopy during cream swallowing. We have called it the "sign of the rising tide" because it describes the backup of cream visible in the hypopharynx as a wave after its complete disappearance. Barium swallow study is necessary to confirm the presumptive diagnosis. This relevant manifestation seems to be specific for Zenker's diverticulum, since it is not observed in other upper esophageal sphincter disorders, and it disappears when surgical treatment is successful.

KEY WORDS — barium swallow study, regurgitation, "sign of the rising tide," videofiberoscopy of swallowing, Zenker's diverticulum.

INTRODUCTION

Zenker's diverticulum is an outpouching of the hypopharyngeal mucosa through the inferior constrictor and cricopharyngeal muscles.[1] Multiple pathogeneses have been suggested; upper esophageal sphincter (UES) dysfunction due to the aging process associated with weakness of Killian's triangle is well acknowledged.[2-5] The diagnosis of Zenker's diverticulum is usually suspected from symptoms such as dysphagia and food regurgitation, and is confirmed by barium swallow study.[6,7] Upper esophageal sphincter function cannot be assessed by indirect laryngologic examination, which may only suggest UES impairment through indirect signs such as pooling of secretions in the pyriform sinuses or aspiration. No specific clinical manifestation of hypopharyngeal diverticulum has been described, since saliva stasis in the hypopharynx may be the result of parietal pharyngoesophageal lesions, isolated impairment of the UES (achalasia), lack of coordination between pharyngeal contraction and UES relaxation, decreased pharyngeal propulsion, or the presence of a Zenker's diverticulum.[8-10]

During the videofiberoscopy (VFS) of cream swallowing,[10-12] we have observed a specific manifestation of pharyngoesophageal diverticulum, which we have called the "sign of the rising tide." In order to correlate this specific fiberoptic manifestation with the existence of a diverticulum (confirmed by barium swallow study), we carried out a prospective study of the results of VFS obtained from a series of 12 patients referred consecutively for Zenker's diverticulum.

Our findings demonstrate that VFS could be used as a supplementary tool to allow the otolaryngologist to suspect Zenker's diverticulum. Videofiberoscopy may provide a more accurate indication for a barium swallow study. It could also be useful in confirming the efficacy of treatment and to follow up patients.

PATIENTS AND METHODS

Twelve patients were included in this prospective study; 7 patients were female, 5 were male, and their mean age was 74.8 years with a range of 51 to 92. The patients were referred consecutively to our institution for swallowing disorders (see Table) from May 1996 to July 1997. The disorders were all related to a pharyngoesophageal diverticulum that was either detected during this examination or diagnosed before. One patient had undergone surgery for Zenker's diverticulum (transcutaneous cricopharyngeal myotomy) 1 year prior to this evaluation. In 1 patient, food esophageal obstruction at the UES had

---

From the Department of Otorhinolaryngology–Head and Neck Surgery, Hôpital Tenon, Faculté de Médecine Saint Antoine, Université Paris VI, Paris, France.

CORRESPONDENCE — Sophie Périé, MD, Service d'Oto-Rhino-Laryngologie et de Chirurgie de la Face et du Cou, Hôpital Tenon, 4, rue de la Chine, 75020 Paris, France.

POPULATION, SYMPTOMS, TREATMENT, AND RESULTS OF VIDEOFIBEROSCOPY OF SWALLOWING BEFORE AND AFTER TREATMENT

			Stasis in Hypopharynx		*"Rising Tide" on VFS*		*Aspiration on VFS*	
Age of Patient (y)	*Symptoms*	*Treatment*	*Preop*	*Postop*	*Preop*	*Postop*	*Preop*	*Postop*
61	Regurgitation	Laser	+	–	+	–	+	–
91	Regurgitation, aspiration, weight loss >5 kg	Laser	+	–	+	–	+	–
80	Regurgitation, blockage, aspiration, weight loss >5 kg	Laser	+	–	+	–	+	–
55*	Regurgitation, blockage, weight loss >5 kg	Laser	–	–	+ (intermittent)	–	–	–
51	Blockage	Laser	+	–	+	+ (slight)	–	–
57	Regurgitation, blockage	Laser	+	–	+	–	+	–
63	Regurgitation, blockage	Cervical myotomy	+	–	+	–	–	–
89	Regurgitation, blockage, aspiration	Cervical myotomy and diverticulopexy	+	?	+	?	–	?
89	Blockage, aspiration pneumonia	Cervical myotomy and diverticulopexy	+	?	+	?	+	?
92	Regurgitation, blockage	Laser	+	?	+	?	–	?
86	Occasional swallowing difficulties	None	+		+		–	
84	Aspiration pneumonia	None	+		+		+	

VFS — videofiberoscopy of swallowing, plus — present, minus — absent, question mark — unknown.

*Cervical myotomy 1 year prior.

led to its extraction by rigid esophagoscopy. The oral food diet had been modified in almost all patients (11 patients), who had adopted a diet of soft or partially blended food.

In all of the patients, a clinical examination and a VFS of swallowing were performed with a flexible laryngoscope (Olympus, ENF type PIII, or Machida, ENT-30 type PIII). Functional assessment of deglutition included an examination during dry and thick cream swallowing. In particular, the following features were recorded: the pooling of saliva or cream in the pyriform sinuses, saliva and/or cream regurgitation, and penetration-aspiration (penetration through the glottis at the time of swallowing). The hypopharyngeal diverticulum was confirmed by a barium swallow study if not previously confirmed in 11 patients. In 1 other, the diverticulum was detected by flexible esophagoscopy.

The VFS was repeated 1 month postoperatively in 7 of the 10 patients who underwent surgical treatment. In addition, we retrospectively reviewed on video 20 randomly chosen patients with isolated UES dysfunction suspected on VFS and confirmed on manometry and/or fluoroscopy.

RESULTS

Analysis of the deglutition by flexible laryngoscopy showed pooling of saliva in the hypopharynx in 11 patients (see Table). In addition, 1 patient also showed a decreased pharyngeal propulsion.

The "rising tide" sign was observed in all patients after cream swallowing, which led to aspiration in 6 of them. It was characterized by the complete disappearance of the swallowed cream from the hypopharynx and pyriform sinuses after completion of the bolus swallowing, followed by a backup of the cream, which returns into the hypopharynx, then disappears again with the next swallow. This succession of movements may be compared with the successive movements of a tide. In contrast, this manifestation was never observed in patients with isolated UES impairment.

Ten patients were treated surgically. Transcutaneous cervical myotomy of the UES was performed in 3 patients, associated with diverticulopexy in 2 of them.[13-16] Seven patients underwent a microendoscopic carbon dioxide laser diverticulotomy.[17-19] Complete or marked improvement of swallowing was obtained in all patients except 1, who sometimes complained of food regurgitation. However, this did not affect his dietary intake. All of the patients were able to return to a normal diet.

In 7 of the 10 patients in whom treatment was performed, VFS was repeated 1 month after surgery.

None of them had saliva or cream hypopharyngeal stasis. A slight "rising tide" sign was observed in the patient who was only partially improved. In others, no rising tide sign was observed. In the improved population, the outcome showed no relapse of the symptoms.

DISCUSSION

The diagnosis of Zenker's diverticulum is usually made by clinical history and barium swallow study. The main clinical manifestation observed in patients with Zenker's diverticulum is usually a pooling of secretions in the pyriform sinuses that is only an indirect sign of UES impairment.[9,10] The VFS can be used as a supplementary tool to study dysphagia during dry swallows and swallowing of foods with various consistencies.[10-12] Its validity has been demonstrated by assessing pharyngeal residues, as well as aspiration episodes, but it does not provide a direct analysis of the UES.[8-10,20,21]

This study has demonstrated that VFS can be used to obtain a presumptive diagnosis of hypopharyngeal diverticulum when special attention is paid to the swallowing of thick cream. The rising tide sign was observed in all of the patients and was only obtained after 3 or 4 cream swallows, which were needed to fill the pouch. This manifestation is due to the spilling of the pouch toward the posterior epilarynx and the upper hypopharynx. It is particularly visible in the retrocricoid area, in which the cream comes back as a wave after the swallowing reflex. Less frequently, the sign may be observed during swallowing of saliva.

Three convincing arguments support the hypothesis that the rising tide sign can be used as a sensitive and specific manifestation of Zenker's diverticulum. First, this sign was observed in all of the patients seen with Zenker's diverticulum, and it was never found in the 20 patients with isolated UES dysfunction. Second, in this series, the presumptive diverticulum was confirmed by a barium swallow study in 11 patients. Thus, the sign's presence could determine whether this examination is necessary. Third, the sign disappeared in patients in whom the surgery was successful. Moreover, 1 patient, who was only partially improved by laser surgery, still exhibited a slight rising tide sign on VFS. In addition, this sign was intermittently found in a patient who had recurrent symptoms of diverticulum 1 year after cervical myotomy. He was then improved by microendoscopic carbon dioxide laser diverticulotomy, and the sign was no longer observed.

We conclude that the "rising tide" sign observed during VFS is a reliable manifestation that can be used to detect Zenker's diverticulum and can be used to evaluate the effectiveness of surgery in these patients. However, barium swallow study remains necessary to confirm the diagnosis of Zenker's diverticulum and to indicate surgery.

ACKNOWLEDGMENT — We are grateful to Dr Gillian Butler-Browne for helpful advice during the preparation of this manuscript.

REFERENCES

1. Payne WS, King RM. Pharyngoesophageal diverticulum. Surg Clin North Am 1983;63:815-24.

2. Cook IJ, Gabb M, Panagopoulos V, et al. Pharyngeal (Zenker's) diverticulum is a disorder of upper esophageal opening. Gastroenterology 1992;103:1229-35.

3. Goyal RK, Martin SB, Shapiro J. The role of cricopharyngeus muscle in pharyngoesophageal disorders. Dysphagia 1993; 8:252-8.

4. Ekberg O, Nylander G. Dysfunction of the cricopharyngeal muscle. Radiology 1982;143:481-6.

5. Cook IJ, Blumbergs JP, Cash K, Jamieson GG, Shearman DJ. Structural abnormalities of the cricopharyngeus muscle in patients with pharyngeal (Zenker's) diverticulum. J Gastroenterol Hepatol 1992;7:556-62.

6. Curtis DJ, Cruess DF, Bert T. The cricopharyngeal muscle: a videorecording review. Am J Roentgenol 1984;142:497-500.

7. Dodds WJ, Logemann JA, Stewart ET. Radiologic assessment of abnormal oral and pharyngeal stages of swallowing. Am J Roentgenol 1990;154:965-74.

8. Logemann JA. Swallowing physiology and pathophysiology. Otolaryngol Clin North Am 1988;21:613-23.

9. Baredes S, Blitzer A, Krespi YP, Logemann JA. Swallowing disorders and aspiration. In: Blitzer A, Sasaki CT, Fahn S, Brin KS, eds. Neurological disorders of the larynx. New York, NY: Thieme Publishers, 1992:201-13.

10. Bastian RW. The videoendoscopic swallowing study: an alternative and partner to the videofluoroscopic swallowing study. Dysphagia 1993;8:359-67.

11. Langmore SE, Schatz K, Olsen N. Fiberoptic endoscopic examination of swallowing safety: a new procedure. Dysphagia 1988;2:216-9.

12. Rosevear WH, Hamlet SL. Flexible fiberoptic laryngoscopy used to assess swallowing function. Ear Nose Throat J 1991;70:498-500.

13. Ellis FH Jr, Schlegel JF, Lynch VP, Payne WS. Cricopharyngeal myotomy for pharyngoesophageal diverticulum. Ann Surg 1969;170:340-9.

14. McKenna JA, Dedo HH. Cricopharyngeal myotomy: indications and technique. Ann Otol Rhinol Laryngol 1992;101: 216-21.

15. Konowitz PM, Biller HF. Diverticulopexy and cricopharyngeal myotomy: treatment for the high-risk patient with a pharyngoesophageal (Zenker's) diverticulum. Otolaryngol Head Neck Surg 1989;100:146-53.

16. Laccourreye O, Menard M, Cauchois R, et al. Esopha-

geal diverticulum: diverticulopexy versus diverticulectomy. Laryngoscope 1994;104:889-92.

17. Holinger LD, Benjamin B. New endoscope for (laser) endoscopic diverticulotomy. Ann Otol Rhinol Laryngol 1987; 96:658-60.

18. Van Overbeek JJM, Hoeksema PE, Edens ET. Microendoscopic surgery of the hypopharyngeal diverticulum using electrocoagulation or carbon dioxide laser. Ann Otol Rhinol Laryngol 1984;93:34-6.

19. Benjamin B, Gallagher R. Microendoscopic laser diverticulotomy for hypopharyngeal diverticulum. Ann Otol Rhinol Laryngol 1993;102:675-9.

20. Langmore SE, Schatz K, Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. Ann Otol Rhinol Laryngol 1991;100:678-81.

21. Kaye GM, Zorowitz RD, Baredes S. Role of flexible laryngoscopy in evaluating aspiration. Ann Otol Rhinol Laryngol 1997;106:705-9.

≈

EUROPEAN SOCIETY OF PEDIATRIC ORL

The Vth International Conference of the European Society of Pediatric ORL will be held July 9-13, 2000, in Graz, Austria. For more information, contact Claire Zwerina, Secretary to Prof Stammberger, ENT-Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43/316/385/3425.

Ann Otol Rhinol Laryngol 108:1999

LOCALIZATION OF ZINC IN THE RAT SUBMANDIBULAR GLAND AND THE EFFECT OF ITS DEFICIENCY ON SALIVARY SECRETION

KOSUKE ISHII, MD
TOCHIGI, JAPAN
MASUMI AKITA, MD
SAITAMA, JAPAN
MASAMI SATO, MD
TOKYO, JAPAN
HIROSHI TOMITA, MD
TOKYO, JAPAN

To clarify the role of zinc in the mechanism of salivary secretion, the effects of zinc deficiency on the morphologic findings and secretory function of the salivary gland were investigated with a rat model of chronic zinc deficiency, prepared by feeding a zinc-deficient diet, and a rat model of acute zinc deficiency, prepared by administration of a zinc chelator, dithizone. In rats with chronic zinc deficiency, the granule production in the granular duct cells was decreased, but the glandular epithelial cells and myoepithelial cells showed no degenerative or other destructive morphologic changes. The degranulation of the granular duct cells and acinar cells in response to acetylcholine hydrochloride seen in control rats was strongly inhibited in rats with acute and chronic zinc deficiency. The contractile response of the actin microfilament bundles in the myoepithelial cells to acetylcholine seen in the control rats was also absent in the zinc-deficient rats. Further, electron microscopy of the submandibular gland stained by Timm's method disclosed prominent zinc localization at the membrane surface, granules, and vesicles of the glandular epithelial cells and in the pits of the myoepithelial cells. These findings suggest that zinc, together with many zinc-dependent enzymes, is closely involved in the production and degranulation of secretory granules in the glandular epithelial cells, and also in the contraction of the myoepithelial cells in the submandibular gland.

KEY WORDS — myoepithelial cells, submandibular gland, Timm's method, zinc.

INTRODUCTION

Zinc is widely distributed in the bone, muscles, liver, prostate, and many other organs and tissues, and its deficiency is known to lead to various zinc deficiency symptoms such as disorders of skin and skin appendages, growth retardation, and taste disorders. In clinical practice, many patients with taste disorders complain of xerostomia, and administration of zinc improves their taste disorders as well as the xerostomia. However, although the localization of zinc and its physiological role in the hippocampus and other organs have been gradually elucidated, little is known about its localization and functional role in the salivary gland. Therefore, we constructed a zinc-deficient rat model and compared the morphologic characteristics of the submandibular gland and its secretory responses to acetylcholine hydrochloride in these rats with those in normal rats. The localization of zinc in the normal rat submandibular gland was also investigated.

METHODS

RATS WITH ZINC-DEFICIENT DIET

Production of Zinc Deficiency. Twelve 4-week-old female Wistar rats were used. The 6 animals in the zinc-deficient group were fed a low-zinc diet (dietary zinc concentration of 2 ppm), and the 6 in the control group, a zinc-supplemented diet (dietary zinc concentration of 100 ppm). The submandibular

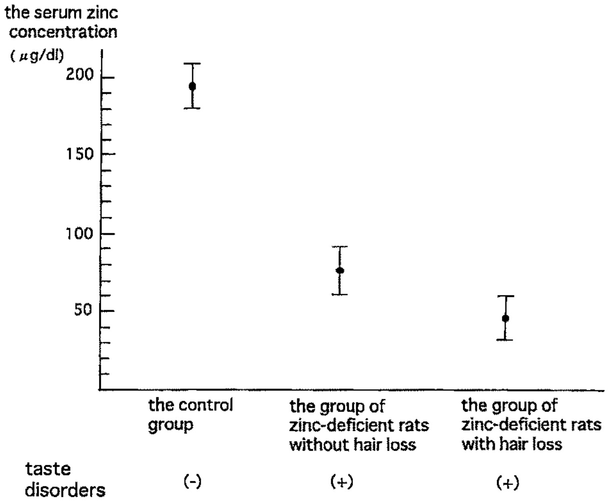


Fig 1. Serum concentrations of zinc and presence or absence of taste disorders in control and zinc-deficient groups. As compared with control group, serum concentration of zinc was decreased in zinc-deficient group, and decrease was greater in subgroup with hair loss than in subgroup without hair loss. Zinc-deficient animals showed taste disorders.

From the Department of Otolaryngology, Saitama Medical Center (Ishii), and the Department of Anatomy (Akita), Saitama Medical School, Saitama, and the Department of Otolaryngology, Tokyo Metropolitan Geriatric Hospital (Sato), and the Department of Otolaryngology, Nihon University School of Medicine (Tomita), Tokyo, Japan.

CORRESPONDENCE — Kosuke Ishii, MD, Dept of Otorhinolaryngology, Jichi Medical School, Minamikawachi-machi, Tochigi-ken 329-04, Japan.

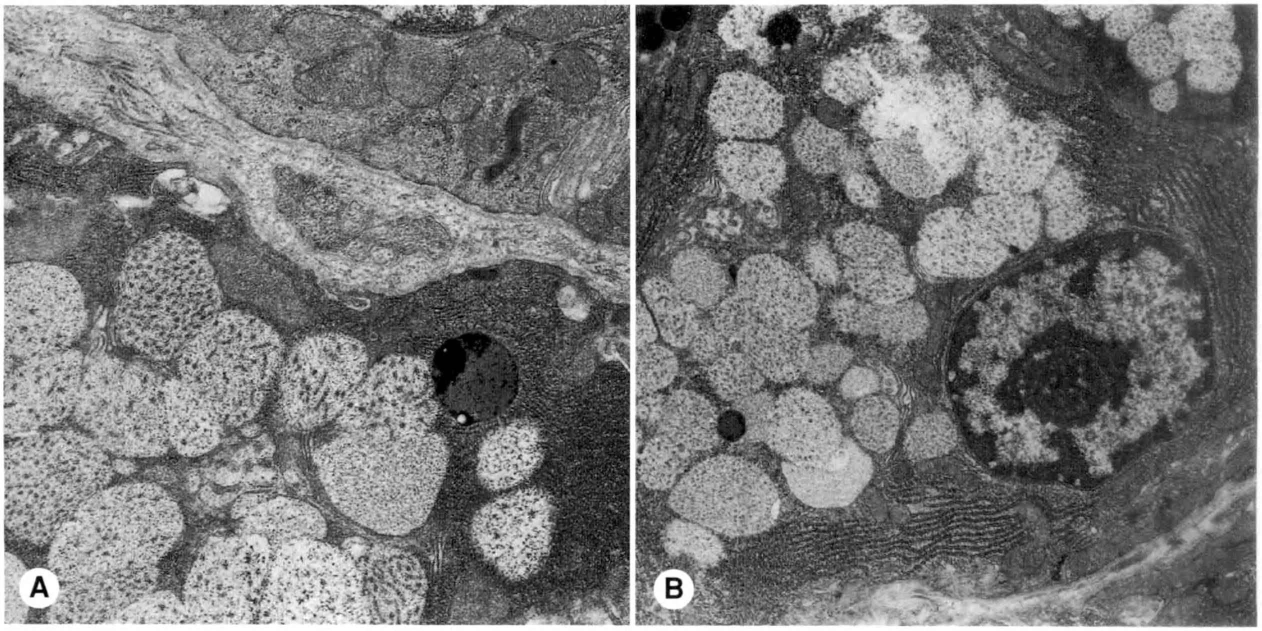


Fig 2. Electron micrographs of glandular epithelial cells in terminal portion of submandibular gland (original ×10,000). A) Control group. B) Zinc-deficient group (without hair loss). No obvious morphologic changes were observed in zinc-deficient group.

glands were removed after 12 weeks of dietary treatment. Before the removal of the submandibular glands, each rat was tested for the presence of taste disorders by the 2-bottle taste aversion paradigm using distilled water and 10^{-6} mol/L quinine hydrochloride. The serum concentration of zinc was also determined in all rats.

Administration of Acetylcholine. Acetylcholine hydrochloride (20 mg/kg) was administered intraperitoneally 15 minutes before the removal of the submandibular glands in half the animals in each group.

Light and Transmission Electron Microscopy. The excised submandibular gland was fixed in 2% glutaraldehyde, post-fixed in osmium tetroxide, dehydrated, embedded in Epon, and cut into sections, and the sections were stained with toluidine blue and examined under a light microscope. Ultrathin sections were also prepared, stained for electron microscopy, and examined with a transmission electron microscope.

Confocal Laser Microscopy. Portions of the submandibular glands from both groups were fixed in 3% paraformaldehyde, freeze-embedded in a tissue compound, and cut into thick frozen sections. The thick sections were incubated with fluorescein isothiocyanate–labeled phalloidin at room temperature for 1 hour and examined under a confocal laser microscope for the 3-dimensional architecture of the

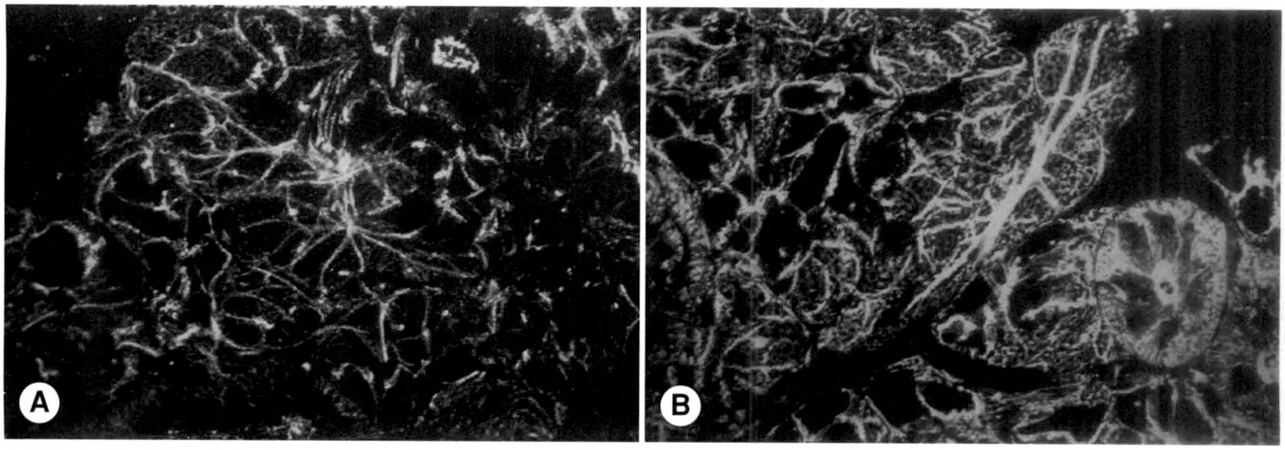


Fig 3. Confocal laser micrographs of actin microfilament bundles in myoepithelial cells of submandibular gland (original ×120). A) Control group. B) Zinc-deficient group (without hair loss). Even in zinc-deficient group, architecture of actin microfilament bundles remained intact.

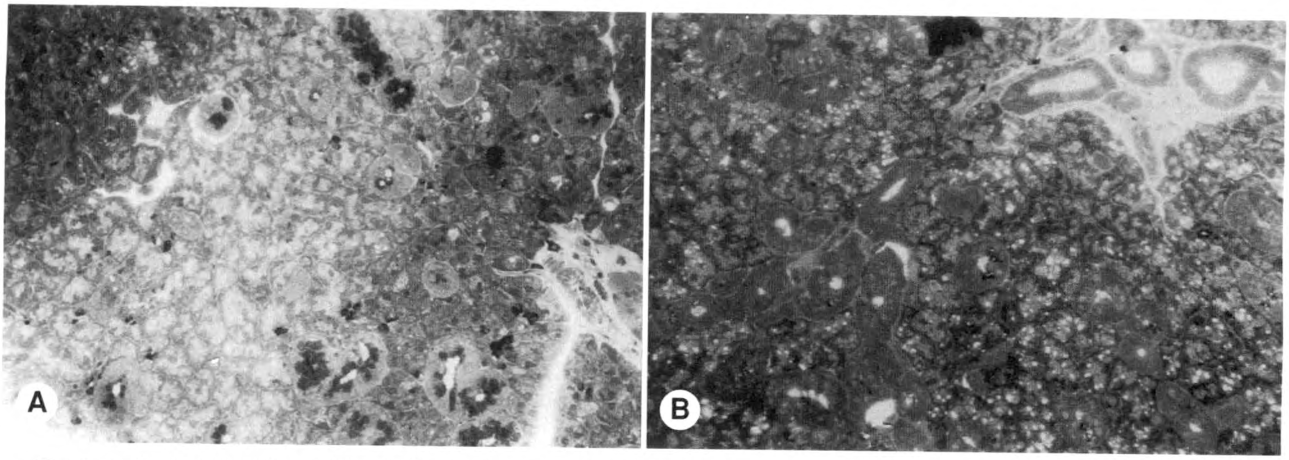


Fig 4. Light micrographs of submandibular gland from control animals (original ×40). A) No treatment. B) Administered acetylcholine hydrochloride. Administration of acetylcholine caused degranulation of granular duct cells and many vacuoles in acinar cells due to degranulation.

actin microfilament bundles in the myoepithelial cells.

RATS TREATED WITH DITHIZONE

Four normal 12-week-old female Wistar rats were used. Fifteen minutes after intravenous administration of the zinc chelator dithizone (50 mg/kg), acetylcholine hydrochloride (20 mg/kg) was administered intraperitoneally, and the submandibular glands were removed 15 minutes later. Two normal female rats were given an intraperitoneal injection of acetylcholine alone, without dithizone, and their submandibular glands were also removed and used as controls.

Determination of Protein Concentration in Saliva. Fifteen minutes after administration of acetylcholine, saliva was collected from rats in both groups, and the protein concentration in the saliva was determined.

Light and Transmission Electron Microscopy. The tissue samples were processed as described above (for light and electron microscopy) and examined by light and electron microscopy.

Confocal Laser Microscopy. The tissue samples were processed as described above (for confocal laser microscopy), and the actin microfilament bundles within the myoepithelial cells were examined for any abnormal morphologic changes under a confocal laser microscope.

LOCALIZATION OF ZINC

Vital Staining With Dithizone. The submandibular glands were removed from 4 normal Wistar rats and, without fixation, incubated in a dithizone solution (dithizone 100 mg, pure alcohol 1 mL, ammonia 4 drops, distilled water 20 mL) for 15 to 30 minutes. The tissues were washed, placed on glass slides, and examined under a light microscope.

Timm's Staining. The submandibular glands removed from 4 normal Wistar rats were fixed in hy-

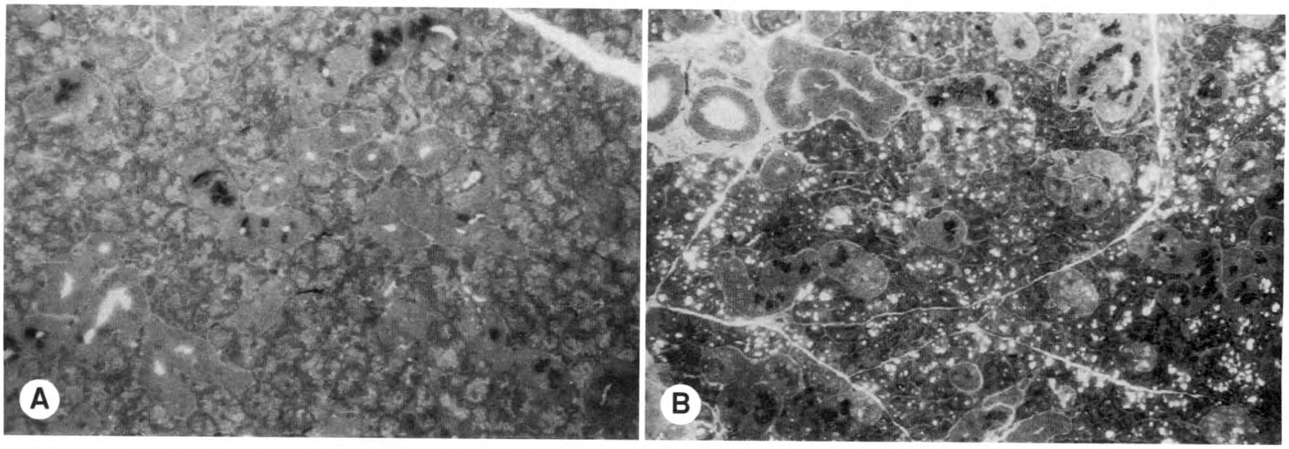


Fig 5. Light micrographs of submandibular gland from zinc-deficient animals (without hair loss; original ×40). A) No treatment. B) Administered acetylcholine. Granule production in granular duct and expulsion of secretory granules were suppressed. Degranulation of acinar cells was not suppressed.

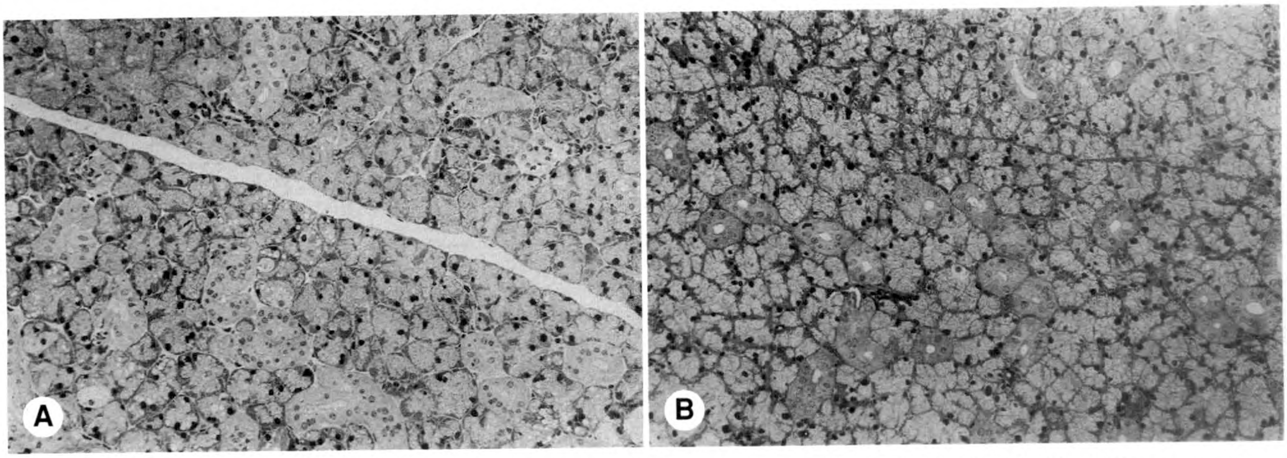


Fig 6. Light micrographs of submandibular gland from zinc-deficient animals (with hair loss; original ×40). A) No treatment. B) Administered acetylcholine. Granular ducts contained almost no granules, and degranulation of acinar cells was strongly suppressed.

drogen sulfide–saturated glutaraldehyde, impregnated with Timm's solution (gum arabic, silver nitrate, hydroquinone, citric acid, distilled water), and post-fixed with osmium tetroxide. After dehydration, the tissues were embedded in Epon, cut into ultrathin sections, and examined under a transmission electron microscope. Control sections were prepared by fixing the tissues in glutaraldehyde that was not saturated with hydrogen sulfide, impregnated with Timm's solution, and processed as described above for transmission electron microscopy.

RESULTS

RATS WITH ZINC-DEFICIENT DIET

The body weight of the zinc-deficient rats was about 80% that of the control rats, indicating impaired growth. In the zinc-deficient group, some animals showed hair loss, and others did not.

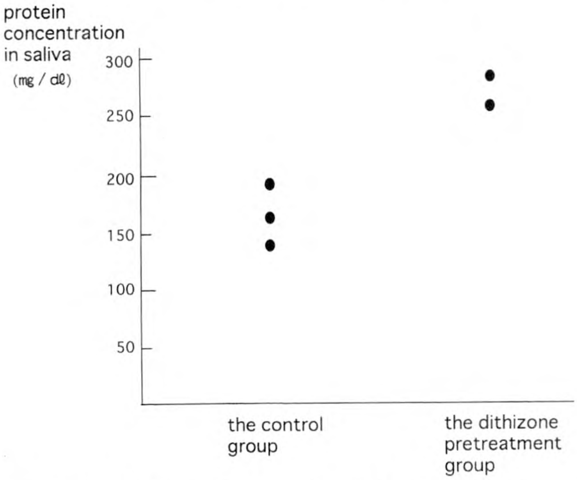


Fig 7. Protein concentrations in saliva after administration of acetylcholine. In dithizone pretreatment group, protein concentration in saliva was higher than that in group not given dithizone.

As compared with the control group, the serum zinc concentration was lower in the zinc-deficient group, and the decrease in serum zinc level was more marked in the animals showing hair loss as compared with those showing no hair loss (Fig 1).

In the 2-bottle taste aversion test with distilled water and 10^{-6} mol/L quinine hydrochloride, the animals in the control group showed no taste disorders, whereas zinc-deficient rats exhibited obvious taste disorders (Fig 1). Histopathologically, the submandibular gland of the zinc-deficient rats showed decreased granule formation within the granular duct cells as compared with that in the control group, but the glandular epithelial cells and myoepithelial cells showed no degenerative or other destructive morphologic features under a light or transmission electron microscope (Fig 2).

By confocal laser microscopy of the myoepithelial cells, the actin microfilament bundles were seen to extend radially in the myoepithelial cytoplasm and

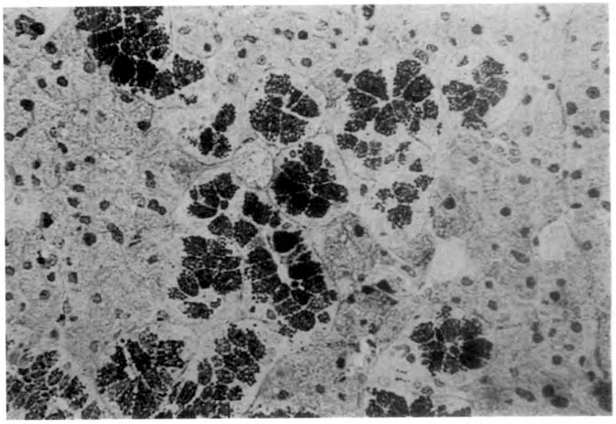


Fig 8. Light micrograph of submandibular gland from normal rat given dithizone followed by acetylcholine (original ×80). Degranulation of both granular duct cells and acinar cells was strongly inhibited.

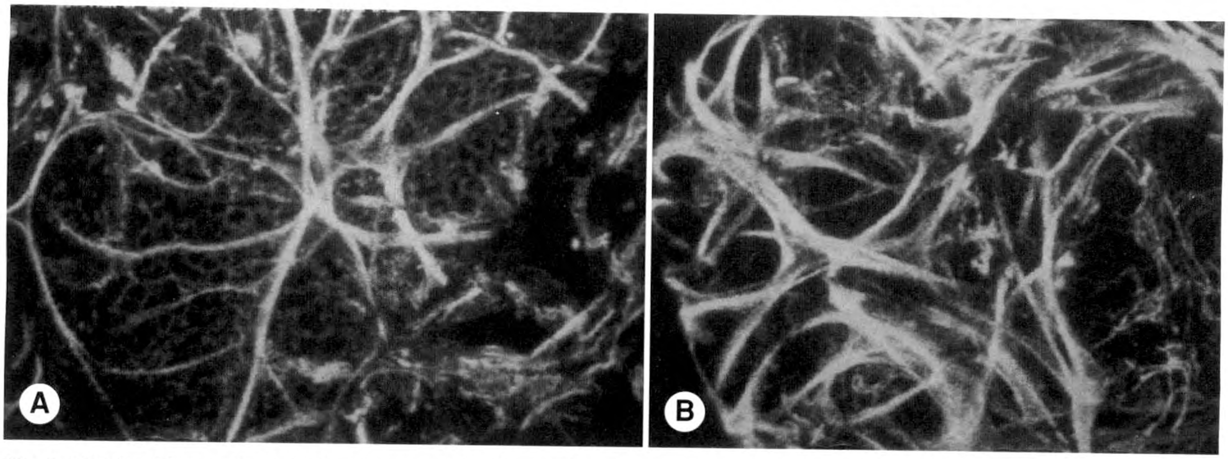


Fig 9. Confocal laser micrographs of actin microfilament bundles in submandibular gland myoepithelial cells in normal rats (original ×240). A) No treatment. B) Administered acetylcholine. Thin actin microfilament bundles extending radially became thicker and more prominent on administration of acetylcholine.

appeared to surround the acini in the control group. In the zinc-deficient group, the normal morphologic configuration of the actin microfilament bundles was preserved as in the control group (Fig 3). In the control group, administration of acetylcholine induced degranulation from the granular duct cells and a marked increase in the number of vacuoles within the acinar cells due to degranulation (Fig 4). In the subgroup of zinc-deficient rats without hair loss, the granule production in the granular duct cells was decreased as compared with that in the control group, and administration of acetylcholine was not followed by degranulation of the granular duct cells. In the acini, however, numerous vacuoles were observed, indicating that the degranulation of the acinar cells was not suppressed (Fig 5). In zinc-deficient rats with hair loss, the granule formation in the granular duct cells was more markedly suppressed than in the subgroup without hair loss, and almost no granules were present in the granular duct cells. Administration of acetylcholine induced no vacuolation even in the acini, indicating that the degranulation was suppressed not only in the granular duct but also in the acinar cells (Fig 6).

RATS TREATED WITH DITHIZONE

In normal rats, administration of acetylcholine without pretreatment with dithizone caused marked salivary secretion, whereas pretreatment with dithizone resulted in a marked reduction in salivary secretion. In the dithizone pretreatment group, the protein content of the saliva was increased compared to that in the group receiving no dithizone pretreatment (Fig 7). Histopathologically, prominent degranulation was observed in the granular ducts and acini in the group receiving no dithizone, whereas degranulation of both the granular duct cells and acinar cells was strongly inhibited in the group receiving dithizone (Fig 8).

Confocal laser microscopy disclosed that in the normal rats receiving no dithizone, thin actin micro-

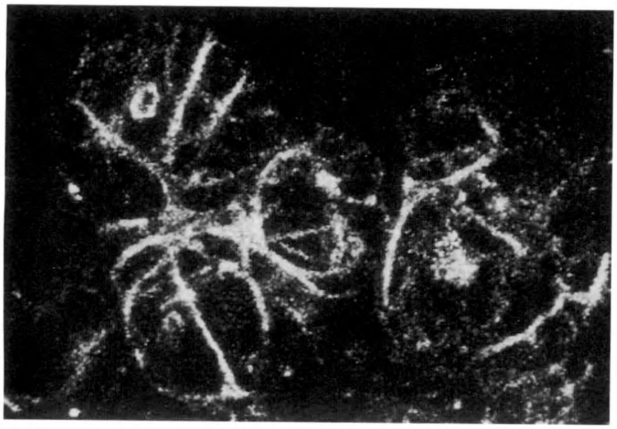


Fig 10. Confocal laser micrograph of actin microfilament bundles in myoepithelial cells in submandibular gland of rat treated with dithizone (original ×240). Pretreatment with dithizone abolished morphologic responses of actin microfilament bundles to acetylcholine.

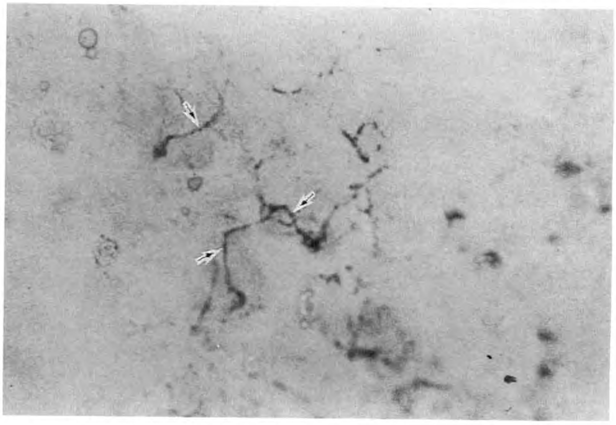


Fig 11. Light micrograph showing localization of zinc in submandibular gland of normal rat treated with dithizone (original ×40). Zinc was localized at surface of acini and intra-acinar spaces (arrows).

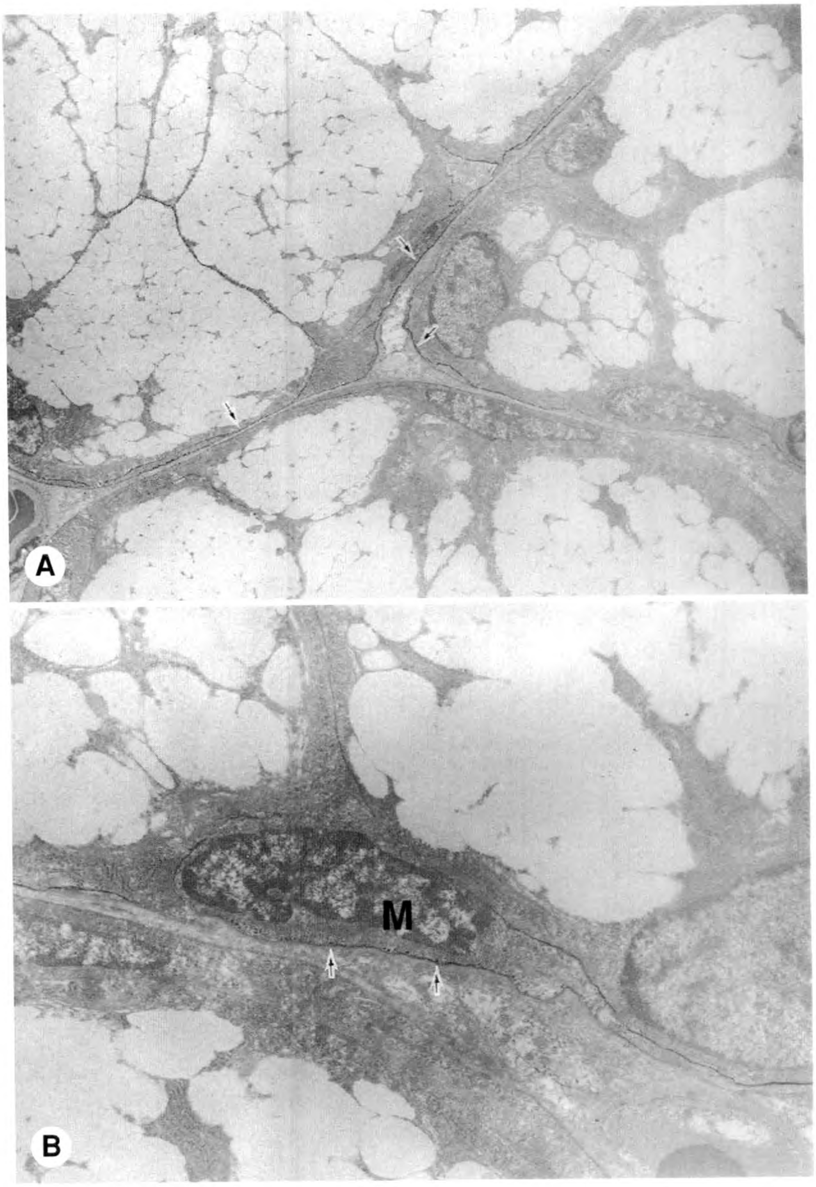


Fig 12. Electron micrographs showing localization of zinc in normal rat submandibular gland (Timm's staining). A) Zinc localized at glandular epithelial cell surface (arrows; original ×6,000). B) Zinc localized at pits of myoepithelial cells (arrows; original ×20,000). M — myoepithelial cell.

filament bundles radially extended within the myoepithelial cells and appeared to surround the acini, and on administration of acetylcholine, the actin microfilament bundles became thickened and appeared to be under more strain (Fig 9). In the group pretreated with dithizone, meanwhile, the actin microfilament bundles did not show the responses to acetylcholine seen in the group receiving no dithizone (Fig 10).

LOCALIZATION OF ZINC

Light microscopy of the tissues stained with dithizone revealed red-staining areas on the acinar surfaces and interacinar spaces (Fig 11). Electron microscopy of the tissues stained by Timm's method disclosed the localization of zinc at the membrane of glandular epithelial cells. Zinc was also localized in the granules and vesicles in the granular duct cells and glandular epithelial cells in the terminal portion. Localization of a large amount of zinc in the pits of the myoepithelial cells was also observed (Fig 12).

DISCUSSION

Henkin et al[1] examined the relationship between saliva and taste disorders in the zinc-deficient state and reported that a zinc protein, gustin, is present in the parotid saliva and is involved in the growth and nutrition of the taste buds; in the zinc-deficient state, the decreased level of gustin in saliva causes pathologic changes in the taste buds and eventually leads to taste disturbances. They noted a close relationship between the salivary concentration of zinc and taste perception, but did not analyze the relationship between salivary function and zinc deficiency. Many patients with taste disorders complain of xerostomia, and we have found that administration of zinc improves xerostomia together with amelioration of the taste disorder. In patients in a zinc-deficient state or with a suspected zinc deficiency, Tanaka[2] examined salivary glandular secretory function by dynamic salivary scintigraphy with ^{99m}Tc-pertechnetate and reported that the salivary glandular secretory ratio was markedly decreased in these patients; administration of zinc for the treatment of taste disorders resulted in the amelioration or resolution of subjective symptoms of xerostomia in 57.9% of the patients. Many zinc-dependent enzymes such as alkaline phosphatase are known to be present in the submandibular gland, and the involvement of zinc in some salivary glandular secretory processes has been suggested by several studies.[3-5]

Zinc is ubiquitously distributed in the bone, muscles, liver, and other systemic body tissues, and its deficiency is known to cause disorders of the skin and skin appendages, as well as growth impairment. In our study, also, the growth retardation in the zinc-deficient group was evident as manifested by their body weight (80% of that of the control group), and hair loss was observed in some animals. However, the glandular epithelial cells and myoepithelial cells in the submandibular gland showed no degenerative or atrophic changes, even in animals exhibiting growth retardation and hair loss. These results therefore confirm that decreased salivary secretion is not due to destruction of the submandibular gland architecture. Kondo et al[6] also reported that in an animal model of zinc deficiency obtained by feeding a zinc-deficient diet, the striated granular duct of the submandibular gland was atrophic due to decreased granule production in the granular duct cells, but the acini remained morphologically intact. Our findings are consistent with their observation.

In the present study, zinc deficiency was associated with decreased cytoplasmic granule formation in the granular duct cells. Christopher et al[7] demonstrated the coexistence of 7S–nerve growth factor complex (NGF) with zinc in the granules in rat submandibular granular ducts. This 7S-NGF is a zinc-containing protein that is stabilized by zinc. The decreased granule formation associated with zinc deficiency in the granular duct cells seen in the present study suggests the role of 7S-NGF in granule formation. Since zinc deficiency did not cause marked morphologic alteration in the submandibular gland, we investigated the effect of zinc deficiency on the salivary glandular secretory function. In the present study, acetylcholine was used to stimulate salivation. Since acetylcholine is a neurotransmitter for both the preganglionic sympathetic nerve fibers and parasympathetic nerve terminals, the intraperitoneal injection of acetylcholine to animals stimulates both the sympathetic and parasympathetic nervous systems. Garrett et al[8] examined the morphologic changes in the rat submandibular gland upon electric stimulation of the sympathetic or parasympathetic nerve fibers innervating the submandibular glands, and reported the appearance of vacuoles due to degranulation in the granular duct cells and acinar cells upon sympathetic stimulation. This finding is consistent with our finding in rats given acetylcholine. Upon electric stimulation of the parasympathetic nerve fibers, an electron microscopic study revealed no degranulation in either the ductular or acinar cells, but the cisternae of the endoplasmic reticulum were slightly dilated. The morphologic changes in the submandibular gland seen in the present study are therefore thought to reflect responses to sympathetic stimulation. Garrett and Harrison[9] described that protein-rich saliva is secreted as a consequence of degranulation, but that protein-poor saliva is secreted via mechanisms other than degranulation.

The degranulation of the secretory cells was suppressed in the zinc-deficient rats. However, degranulation was suppressed only in the granular duct cells in the subgroup without hair loss, whereas it was suppressed in both the granular ducts and acinar cells in the subgroup showing hair loss. Because the serum zinc level was reduced more markedly in the animals with hair loss than in those without hair loss, the mechanism mediating the degranulation of the granular duct cells is thought to be more zinc-dependent than that mediating the degranulation of the acinar cells.

Our first experiment was performed on zinc-deficient rats prepared by feeding a low zinc diet. In this model, which is a clinically useful model of human zinc deficiency syndromes, the rats became malnourished as the serum level of zinc decreased and also showed hypoproteinemia and imbalance of other nutritional components and electrolytes, but the rats were not completely zinc-deficient. In the second experiment, therefore, rats were administered dithizone, a chelator of zinc, to obtain a completely zinc-deficient rat model, and we examined their submandibular glands for secretory function and morphologic changes. In dithizone-treated rats, the degranulation of the granular duct cells and acinar cells in response to acetylcholine was strongly inhibited. Since the saliva secreted via the degranulation mechanism is protein-rich, as described above, the effect of zinc deficiency on the secretion of protein-poor saliva remains unknown from these results alone. In the second experiment, however, acetylcholine-stimulated salivary secretion was markedly decreased by the pretreatment with dithizone, but the protein content in the saliva rather increased. This implies that the acetylcholine-induced increase in salivary secretion is mainly due to the increase in protein-poor saliva and that the secretion of this protein-poor saliva is also strongly inhibited by dithizone. Thus, zinc appears to be closely involved in the secretion of both the protein-rich and protein-poor components of saliva.

In addition to the glandular epithelial cells, the myoepithelial cells also play an important role in the secretion of saliva. Acetylcholine induced marked morphologic changes in the actin microfilament bundles in the myoepithelial cells of the normal submandibular gland, as shown in Fig 9. In the present study, the pretreatment with dithizone abolished these morphologic responses of the actin microfilament bundles to acetylcholine, suggesting the involvement of zinc in the contractile activity of the myoepithelial cells.

The localization of zinc in the submandibular gland had not been examined at the electron microscopic level. In the present study, zinc was localized on the membrane surfaces and in the granules and vesicles of glandular epithelial cells and in the pits of myoepithelial cells. It is known that zinc metalloenzymes such as alkaline phosphatase and carbonic anhydrase are present in the myoepithelial cells and glandular epithelial cells. Chaudry et al[3,4] and Gandor et al[5] reported that in zinc-deficient rats, these enzyme activities in the submandibular gland decreased to 44% and 26%, respectively, of control values. Zinc is thought to be involved in the salivary secretion mediated by these enzymes, but more detailed studies are needed to clarify the secretory mechanism involving zinc. The light and electron microscopic studies of the myoepithelial cells of the human salivary glands[9,10] indicated the absence of alkaline phosphatase activity but the presence of Ca^{2+}-stimulated adenosine triphosphatase (Ca^{2+}-ATPase) activity, suggesting the involvement of this enzyme in the myoepithelial cell contraction. It was also found that in a zinc-deficient state, the activity of calmodulin, a calcium-binding protein, is decreased and Ca^{2+}-ATPase activity in rat and pig erythrocyte membranes is also decreased.[11] Decreased calmodulin activity in the muscles and testis of zinc-deficient rats has recently been reported.[12,13] Although there is no report about decreased calmodulin activity in the submandibular gland, it is speculated that zinc deficiency reduces Ca^{2+}-ATPase activity via the mediation of decreased calmodulin activity, leading to reduced contractile activity of the myoepithelial cells.

Most studies on the relationship between zinc and the salivary glands have indicated that zinc deficiency suppresses the growth of the glandular epithelial cells and secondarily causes salivary hyposecretion. However, the present study suggests the involvement of zinc in the very early stages of salivary secretory processes such as formation of secretory granules and degranulation of the glandular cells and myoepithelial contractions. Zinc is known to be concentrated in the synaptic structures of mossy fibers in the hippocampus, and there are many published studies on the role of zinc in this area. The functional role of zinc as a neurotransmitter has also been suggested.[14] In the salivary glands, also, zinc appears to be closely involved in secretory functions, rather than functioning only as a growth factor for the glandular epithelial cells and myoepithelial cells.

REFERENCES

1. Henkin RI, Lippoldt RE, Bilstad J, Edelhoch H. A zinc protein from human parotid saliva. Proc Natl Acad Sci USA 1975;72:488-92.

2. Tanaka M. Secretory function of the salivary gland in patients with taste disorders. Correlations between zinc deficiency and secretory functions of the salivary glands. J Otolaryngol Jpn 1994;97:485-93.

3. Chaudry IM, Meyer J. Response of the submandibular gland of the rat to nutritional zinc deficiency. J Nutr 1979;109: 316-20.

4. Chaudry IM, Gandor DW, Gerson SJ. Reduction of carbonic anhydrase in the submandibular salivary glands of zinc-deficient rats. Arch Oral Biol 1981;26:399-402.

5. Gandor DW, Fanslow DJ, Meyer J. Effects of zinc deficiency on developmental changes in alkaline phosphatase and carbonic anhydrase activities in the submandibular gland of the rat. Arch Oral Biol 1983;28:609-14.

6. Kondo I, Ozono S, Sato K, Ito Y. Histology of the submandibular gland in experimentally induced zinc deficient mice. Bull Kanagawa Dent Coll 1989;17:159-63.

7. Christopher J, Frederickson F, Perez-Clausell J, Danscher G. Zinc-containing 7s-NGF complex. Evidence from zinc histochemistry for localization in salivary secretory granules. J Histochem Cytochem 1987;35:579-83.

8. Garrett JR, Suleiman AM, Anderson LC, Proctor GB. Secretory responses in granular ducts and acini of submandibular glands in vivo to parasympathetic or sympathetic nerve stimulation in rats. Cell Tissue Res 1991;264:117-26.

9. Garrett JR, Harrison JD. Alkaline-phosphatase and adenosine-triphosphatase histochemical reactions in the salivary glands of cat, dog and man with particular reference to the myoepithelial cells. Histochemie 1970;24:214-29.

10. Cossu M, Lantini MS, Puxeddu P, Riva A. Cytochemical localization of ouabain-sensitive, K^+-dependent p-nitrophenylphosphatase and Ca^{++}-stimulated adenosine triphosphatase activities in human parotid and submandibular glands. Histochemie 1984;81:221-5.

11. Johanning GL, Browning JD, Bobilya DJ. Effect of zinc deficiency on enzyme activities in rat and pig erythrocyte membranes. Proc Soc Exp Biol Med 1990;195:224-9.

12. Law JS, McBridge SA, Graham S, Nelson NR, Slotnick BM, Henkin RI. In vivo effects of zinc deficiency on calmodulin concentrations in selected rat tissue. Life Sci 1987;41:2597-606.

13. Roth HP, Kirchgessner M. Calmodulin activity in tissues of Zn- and Ca-deficient rats. J Trace Elem Electrolytes Health Dis 1991;5:213-7.

14. Perez-Clausell J, Danscher G. Release of zinc sulphide accumulations into synaptic clefts after in vivo injection of sodium sulphide. Brain Res 1985;362:358-61.

≈

FUNCTIONAL AESTHETIC NASAL SURGERY

The 17th International Course in Functional Aesthetic Nasal Surgery will be held in English, June 15-18, 1999, in Utrecht, the Netherlands. For information, contact Ms. T. Kortleve, Dept of ORL, University Hospital Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands; telephone +31-30-2506645; fax +31-30-2541922; e-mail t.kortleve@kmb.azu.nl.

Ann Otol Rhinol Laryngol 108:1999

EFFECT OF SLEEP STATE ON THE LARYNGEAL CHEMOREFLEX IN NEONATAL PIGLETS

SUZANNE S. CLELAND-ZAMUDIO, MD
PORTLAND, OREGON
MARK MAHOWALD, MD
MINNEAPOLIS, MINNESOTA
GEORGE S. GODING, MD
MINNEAPOLIS, MINNESOTA
KERRI J. PERNELL, MS
MINNEAPOLIS, MINNESOTA

The laryngeal chemoreflex (LCR) is a brain stem–mediated response that is a potential mechanism for sudden infant death syndrome. The vast majority of sudden infant death occurs during sleep, yet it remains to be established whether there is a particular sleep state that makes an infant animal more susceptible to apneic events via the LCR. The purpose of this study was to investigate the LCR during different sleep states in the neonatal piglet. In this study, continuous physiologic monitoring and electroencephalographic, electro-oculographic, and electromyographic techniques were utilized to study neonatal piglets during a hypnotic induced sleep model. Propofol drip anesthetic was utilized to provide an anesthetic state and was titrated for dose-dependent sedation. The LCR was initiated in 11 animals during quiet sleep, rapid eye movement sleep, and the anesthetic state. Baseline respiratory and cardiovascular responses were measured. Durations of apnea were recorded and compared. This study found that despite known physiologic differences in respiratory control during different sleep states as compared to the anesthetic state, there appears to be no increased risk of profound apnea in one state versus another in piglets 19 to 28 days old.

KEY WORDS — apnea, laryngeal chemoreflex, rapid eye movement sleep, sleep state, sudden infant death syndrome.

INTRODUCTION

The primary purpose of the larynx is to protect the lower respiratory tract from aspiration of swallowed or refluxed materials in the pharynx. The proper maturation of protective respiratory control mechanisms is essential to normal development of an infant. Dysfunction in associated control systems has been implicated in sudden infant death syndrome (SIDS)[1,2] and in gastroesophageal reflux–induced apnea.[3,4] The laryngeal chemoreflex (LCR) is a brain stem–mediated response whereby chemical stimulation of the infant larynx is associated with reflexive apnea, hypotension or hypertension, bradycardia, and reflex glottic closure that may be fatal.[5-8] The severity of the LCR is dramatically influenced by the age of the animal.[2] As with SIDS, there is a specific period of postnatal maturation and development during which a fatal or near-fatal response to the LCR can occur. The LCR appears to be a manifestation of the sensitivity of the cardiorespiratory system during development.

The vast majority of sudden infant deaths occur during sleep. Polysomnographic studies of infants who later perished of SIDS revealed frequent and prolonged apnea, mainly during rapid eye movement (REM) sleep.[9] The control of breathing during sleep has been extensively reviewed,[10-12] and there is a growing realization that dysfunction of brain stem respiratory control mechanisms during sleep may produce changes in autonomic nervous system–mediated respiratory activity.[13] The variations in physiologic respiratory mechanisms that exist during sleep could give certain states increased susceptibility to apneic events in general or fatal apneic events. Although it is known that control over respiratory mechanisms at the central nervous system level is altered during sleep, there have been few comparative studies investigating the LCR during quiet sleep and REM sleep.[8,14,15] Previous studies on the LCR in infant animals have required the use of anesthetized animals or were observational in nature, with a limited age range used, or required invasive physiologic monitoring. With the ability to use a dose-dependent hypnotic agent such as intravenous propofol, we can now achieve polysomnographic evidence of sleep states in neonatal piglets that correlate to human infant polysomnographic findings.[16,17]

The purpose of this project was to investigate the LCR model under different levels of arousal as defined by polysomnographic criteria. In particular, the

---

From the Departments of Otolaryngology–Head and Neck Surgery (Cleland-Zamudio, Goding, Pernell) and Neurology (Mahowald) and the Minnesota Regional Sleep Disorders Center (Mahowald), Hennepin County Medical Center, Minneapolis, Minnesota. Dr Cleland-Zamudio is currently in private practice in Portland, Oregon. Funded by a grant from the Minnesota Medical Research Foundation. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Minnesota Medical Research Foundation.

CORRESPONDENCE — George S. Goding, MD, Dept of Otolaryngology, 701 Park Ave S, Minneapolis, MN 55415.

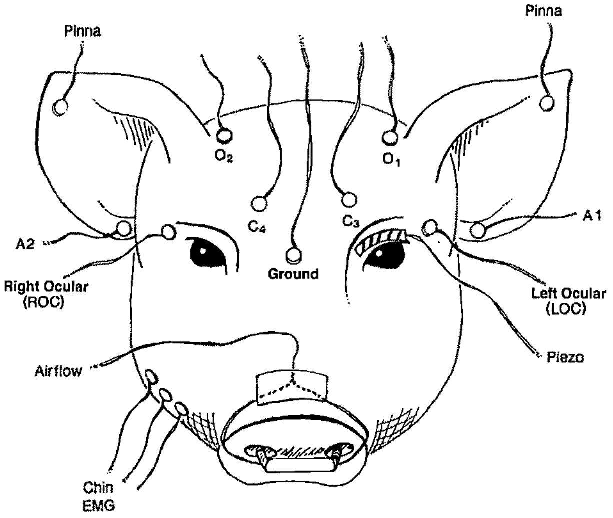


Fig 1. Lead placement for polysomnographic study.

study examined whether a state-dependent difference in susceptibility to an apneic response exists during sleep.

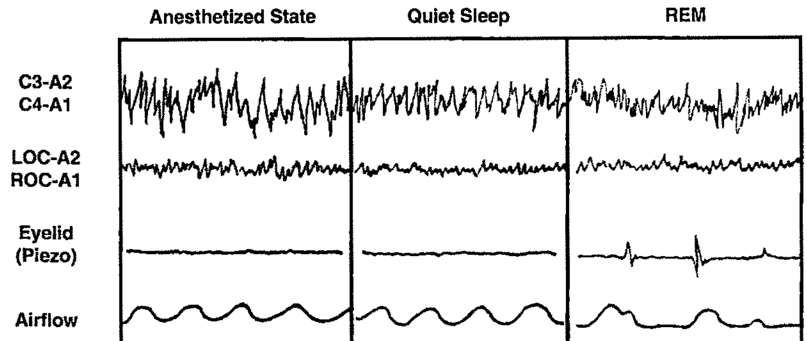
METHODS

Subjects. Twenty white male piglets, 14 to 29 days old, ranging in weight from 2.8 to 5.9 kg, were used in this study. Our proposed study design and animal care protocol were approved by the Animal Care and Use Committee of the Minneapolis Medical Research Foundation. Several pilot animals were used for observation and study of infant porcine sleep patterns, testing of the LCR stimulation protocol, and propofol titration.

Anesthesia. Induction anesthesia was initiated with intramuscular injection of ketamine hydrochloride (35 mg/kg) and xylazine hydrochloride (5 mg/kg). This was administered in a single dose allowing 30 to 40 minutes for the animals to be weighed and shaved around the forehead, face, chin, and nuchal region, and allowing time for placement of an intravenous ear catheter. Animals were hydrated with a 250-mL bolus of intravenous normal saline as physiologic monitors were placed. Propofol (Diprivan) drip anesthesia was initiated at 110 to 130 µg/kg per minute. An anesthetic state was defined as the presence of rhythmic, spontaneous respirations, absence of corneal and pain reflexes, lack of head and extremity movement, and presence of cyclic background cortical slowing activity. Once LCR stimulation was performed under the anesthetic state, the titration was lowered to achieve light sedation and allow for sleep state presentation. Light sedation was hallmarked by electroencephalography (EEG) evidence of markedly reduced or eliminated background cortical sinusoidal wave activity and increased frequency and decreased amplitude of EEG activity. If animals were aroused prematurely, they were given a 10-mg bolus of propofol and the drip was reinitiated at a higher rate.

Physiologic and Polysomnographic Preparation and Monitoring. Following induction of anesthesia, all animals underwent placement of a 24-gauge intravenous polyethylene catheter percutaneously into a superficial auricular vein. Each animal underwent placement of a 22- or 24-gauge catheter into the right or left femoral artery for blood pressure monitoring and arterial access for blood gas sample analysis. A Hewlett Packard monitor (model 78205B) was used to monitor systolic and diastolic blood pressure via a pressure transducer. Subdermal abdominal needle electrodes were used to monitor respiratory rate (based on chest wall muscular effort). Respiratory rate was monitored with a Hewlett Packard respiration monitor (model 782025B). Due to the evidence that hypoxic conditions can directly affect the severity and duration of apnea seen with LCR stimulation,[18] supplemental oxygen was delivered in a blow-by fashion to maintain a hemoglobin saturation above 95%. Saturation was monitored via an ear transducer clamp on a Nellcor 200 pulse oximeter. Arterial pH measurements were taken prior to initial stimulation and were repeated prior to subsequent stimulations if an animal had a resuscitation event or if maintenance of hemoglobin saturation was difficult. Arterial pH readings below 7.3 disqualified an animal from further stimulations. Temperature was continuously recorded with a rectal probe connected to a Hewlett Packard temperature module. Animal temperature was maintained at 37.0°C to 38.6°C with a heating pad under the animal to avoid temperature effects on LCR, since hyperthermia has been shown to affect the LCR response.[19]

Electrocardiography (ECG) and cortical electrical activity were continuously monitored with metal cup electrodes that were applied with collodion (an ether-based adhesive) and checked to ensure a maximum impedance of 10 kilo-ohms. Electroencephalographic lead placement was done in the standard C4/A1, C3/A2, C3/O2, and C4/O1 positions (Fig 1). Electro-oculography (EOG) will be done with placement at the lateral canthi referencing to A1 bilaterally. Electromyography (EMG) of the submental, nuchal, leg, and pinna musculature was performed. The signals were amplified by a Grass polygraph (model 8-18D) and bandpass-filtered to attenuate frequencies outside the following ranges: EEG and EOG, 0.3 to 35 Hz; EMG, 5.0 to 70 Hz; and ECG, 1.0 to 15.0 Hz. Nasal airflow and eyelid movements were recorded on the polysomnograph from an Easyflow disposable airflow thermocouple (EPM systems) and a Healthdyne piezoelectric eyelid move-



Sleep State Criteria	Anesthetized State	Quiet Sleep	REM
	• Occasional rapid burst pattern • Rhythmic cortical slow sinus wave pattern • Amplitude high • Low frequency • Rhythmic spontaneous respiration • Lack of gross motor movement • Lack of eyelid movement • Lack of corneal reflex • Lack of pain stimulus to tail clamp	• Diminished or absent sinus wave pattern • Amplitude intermediate • Frequency intermediate • Regular breathing • Lack of gross motor movement • Lack of eyelid movement • Quiet snoring noises	• Diminished or lack of sinus wave pattern • Amplitude low • High frequency • Irregular breathing • Eyelid motion • Evidence of muscle tension on extremities and pinna

REM - Rapid Eye Movement. 6 of 12 polysomnographic channels shown.

Fig 2. Sleep state criteria based on electroencephalography, electro-oculography, electromyography, piezoelectric monitoring, and airflow monitoring.

ment transducer (No. 232), respectively. Polysomnographic data were recorded on a strip chart at a paper speed of 10 or 15 mm/s (alternated for comparison). An integrity check of the electrodes was done prior to start by touch during recording.

Laryngeal Chemostimulation Protocol. An 8F neonate nasogastric tube was passed through the nasal passage of the piglet until the tip was seen at the edge of the soft palate by direct laryngoscopy. Prior to each trial, baseline blood gas measurements, blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation were recorded. When the appropriate state was confirmed by observational and polysomnographic techniques lasting greater than 30 seconds, the LCR was stimulated. Chemical stimulation of the LCR was performed by rapid injection of 3 to 4 mL of normal saline (titrated to a pH of 3 with hydrochloric acid). It was given via the nasal catheter onto the laryngeal mucosa and epiglottis. The animal was allowed to recover spontaneously until apnea length reached 120 seconds or until blood pressure fell below 60 mm Hg. Each animal was given a minimum of 15 to 30 minutes' recovery time between stimulations. Baseline physiologic measurements were recorded 15 seconds prior to chemostimulation, during stimulation, and until recovery was achieved. Respiratory rate, blood pressure, oxygen saturation, and airflow were recorded on FM tape and digitalized to a Macintosh IIci computer with Labview 3.0 software. The LCR stimulations were performed during 1) the anesthetic state, 2) quiet sleep with light sedation (non-REM), and 3) REM sleep with light sedation. Sleep state criteria are shown in Fig 2.

RESULTS

Of the 20 piglets tested, all 3 levels of arousal were obtained in 11 piglets. The other 9 piglets were not analyzed further. The animals achieved anesthesia in titrated ranges of propofol at 110 to 140 μg/kg per minute. Once anesthetic data were obtained, sleep patterns were observed in titration ranges of 55 to 95 μg/kg per minute.

The polysomnography study from a 22-day-old piglet is shown in Fig 2. Only 6 of the 12 channels are displayed. The 11 pigs that completed the study ranged in age from 19 to 28 days old and weighed 2.9 to 4.9 kg. Apnea duration was defined as the time between laryngeal stimulation and the resumption of breathing. The apnea duration ranged from 22 to 108 seconds in the anesthetic state, 7 to 105 seconds in quiet sleep, and 30 to 120 seconds in REM sleep. The average duration of apnea (±SD) was 66.27 ± 29.76 seconds for the anesthetic state, 52.81 ± 38.02 seconds for quiet sleep, and 60.23 ± 28.14 seconds for REM sleep. A 1-factor repeated measures analysis of variance looking at apnea lengths in different states showed that the apnea durations were strikingly similar ($p = .637$). All animals experienced variable periods of hypertension or hypotension, oxygen desaturation, and bradycardia. Only 1 of 33 trials caused a profound fatal apnea under REM sleep. Three of 33 trials required formal resuscitation measures, with all 3 arrests occurring in the same piglet. Arterial pH gas measurements of all 3 states were obtained in only 8 of the 11 piglets, due to equipment malfunction.

DISCUSSION

In this study we found that in 19- to 28-day-old piglets there appears to be no difference in susceptibility to an apneic event among the anesthetic state, quiet sleep, and REM sleep.

The piglet is an established model for the LCR,[5,20,21] as well as for infant sleep.[16,17,22] Limitations of this model include need for careful titration of drip-controlled sedation to avoid early arousal, a limited testing period due to the effect of prolonged propofol exposure, and the need for experienced polysomnographic technicians. With the brief durations of REM sleep that these animals often have (15 to 45 seconds at a time), REM sleep was difficult to recognize in time for stimulation, and so, some animals were excluded for not being able to achieve all 3 sleep states.

Propofol itself may have an effect on sleep states. There is evidence to suggest that propofol may affect the soft palate and pharyngeal tone in human patients lying supine.[23] Although our test animals were positioned on their side and sleep was achieved in only hypnotic or sedation doses, there may have been associated pharyngeal relaxation that could affect the response to LCR. If the propofol had affected pharyngeal tone to a significant level, it would seem likely that the polysomnographic and observational data would have reflected evidence for central or obstructive apnea during sleep, and this was not seen.

The half-life of ketamine is 1 to 2 hours in children and is believed to be less in infants because of increased metabolism.[24,25] Xylazine is a sedative muscle relaxant with a half-life of 24 minutes.[25] Experience in our laboratory has shown that the ketamine-xylazine combination provides 45 to 60 minutes of intramuscular sedation, after which time, arousal is rapid. This induction method was chosen because of the ease of intramuscular administration, the rapid onset of sedation, and sufficient time for necessary catheter and monitor placement. After animals showed signs of arousal, propofol was administered intravenously and drip anesthesia was started. An average time of 3.5 to 4 hours was allowed from the time of induction anesthesia to the start of formal monitoring in order to ensure no effect of induction anesthesia on sleep or anesthetic states. By this method, we ensured that ketamine was effectively out of the system prior to stimulation.

Propofol is one of a series of alkyl phenols that has been studied in use with laboratory animals, including piglets.[26-28] It is known to provide rapid-onset anesthesia, titratable dose-related sedation, and rapid arousal with limited effect on upper airway tone.[29,30] Its half-life is 1 to 2 minutes or less in infant animals and varies with metabolic rate. Sleep states achieved during pilot studies were reviewed with a neonatal polysomnographic specialist and were consistent with those seen in human neonate sleep.

The control of respiration during sleep states has been a source of study for decades, yet the cause of many sleep-related respiratory disturbances, such as SIDS, remains elusive. Studies by Phillipson[10] have shown that respiratory control mechanisms during sleep are distinctly different for REM sleep and non-REM sleep (quiet sleep). During REM sleep, respiratory regulation appears to be affected more by laryngeal, brain stem, and cortical influences. In non-REM sleep (quiet sleep), arterial chemoreceptors play a predominant role.[10-12]

The irregular and shallow ventilatory responses seen in the normal REM sleep pattern have implicated REM sleep as a theoretically vulnerable state for apnea. In a review of infant apnea by Spitzer and Fox,[9] it was believed that more frequent spontaneous apnea events occurred during REM sleep. In a study of adult dogs, Sullivan et al[15] found laryngeal stimulation during REM sleep to be associated with a longer apnea and a depressed arousal response as compared to slow-wave sleep (quiet). Marchal et al[8] looked at the LCR response during sleep states in nonsedated neonatal lambs and, in agreement with our findings, found no difference in REM and quiet sleep apnea responses.

What we know is that according to polysomnographic evidence of infant sleep as modeled by the neonatal piglet, there was no difference among sleep states in duration or severity of apnea.

ACKNOWLEDGMENTS — We thank Linnea Putz, Fernando Torres, and the Minnesota Regional Sleep Disorders Center for their assistance in this study.

REFERENCES

1. Downing SE, Lee JC. Laryngeal chemosensitivity: a possible mechanism for sudden infant death. Pediatrics 1975;55:640-9.

2. Freed GE, Steinschneider A, Glassman M, Winn K. Sudden infant death syndrome prevention and an understanding of selected clinical issues. Pediatr Clin North Am 1994;41:967-90.

3. Byard RW, Moore L. Gastroesophageal reflux and sudden infant death syndrome. Pediatr Pathol 1993;13:53-7.

4. Jeffery HE, Page M, Post EJ, Wood AK. Physiological studies of gastroesophageal reflux and airway protective responses in the young animal and human. Clin Exp Pharmacol

Physiol 1995;22:544-9.

5. Lee JB, Stoll B, Downing SE. Properties of the laryngeal chemoreflex in neonatal pigs. Am J Physiol 1977;233:30-7.

6. Wetmore RF. Effects of acid on the larynx of the maturing rabbit and their possible significance to the sudden infant death syndrome. Laryngoscope 1993;103:1242-54.

7. Boggs DF, Bartlett D. Chemical specificity of the laryngeal apneic reflex in puppies. J Appl Physiol 1982;53:455-62.

8. Marchal F, Corke BC, Sundell H. Reflex apnea from laryngeal chemo-stimulation in the sleeping preterm newborn lamb. Pediatr Res 1982;16:621-7.

9. Spitzer AR, Fox WW. Infant apnea. Pediatr Clin North Am 1986;33:561-81.

10. Phillipson EA. Control of breathing during sleep. Am Rev Respir Dis 1978;118:909-39.

11. Remmers JE. Effect of sleep on control of breathing. International review of physiology. Int Rev Physiol 1981;23:111-47.

12. Schechtman VL, Harper RM. The maturation of correlations between cardiac and respiratory measures across sleep states in normal infants. Sleep 1992;15:41-7.

13. Kinney HC, Filiano JJ, Sleeper LA, Mandell FM, Valdes-Dapena M, White WF. Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. Science 1995;269:1446-50.

14. Post EJ, Wood AK, Page M, Jeffery HE. A method for simultaneous physiologic and radiographic recordings from sleeping neonatal pigs. Sleep 1995;18:309-16.

15. Sullivan CE, Murphy E, Kozar LF, Phillipson EA. Waking and ventilatory responses to laryngeal stimulation in sleeping dogs. J Appl Physiol 1978;45:681-9.

16. Anders T, Emde R, Parmalee A. A manual of standardized terminology, techniques and criteria for scoring sleep and wakefulness in newborn infants. Los Angeles, Calif: UCLA Brain Information Service/BRI Publications Office, 1971.

17. Robert S, Dallaire A. Polygraphic analysis of the sleep-wake states and the REM sleep periodicity in domesticated piglets. Physiol Behav 1986;37:289-93.

18. Lanier B, Richardson MA, Cummings C. The effect of hypoxia on laryngeal reflex apnea: implications for sudden infant death. Otolaryngol Head Neck Surg 1983;91:597-604.

19. Haraguchi S, Fung RQ, Sasaki CT. Effect of hyperthermia on laryngeal closure reflex. Implications in the sudden infant death syndrome. Ann Otol Rhinol Laryngol 1983;92:24-8.

20. Goding GS, Richardson MA, Trachy RE. Laryngeal chemoreflex: anatomic and physiologic study using the superior laryngeal nerve in the piglet. Otolaryngol Head Neck Surg 1987; 97:28-38.

21. Rimell F, Goding GS Jr, Johnson K. Cholinergic agents in the laryngeal chemoreflex model of sudden infant death syndrome. Laryngoscope 1993;103:623-30.

22. Scott SC, Inman JDG, Moss IR. Ontogeny of sleep/wake states and cardiorespiratory behavior in unanesthetized pigs. Respir Physiol 1990;80:83-102.

23. Mathru M, Esch O, Lang J, et al. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. Anesthesiology 1996;84:273-9.

24. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of IM and oral ketamine. Br J Anaesth 1981;53:805-9.

25. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. Br J Anaesth 1983;55: 1107-11.

26. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. Anesthesiology 1989;71:260-77.

27. Ramsey DE, Aldred N, Power JM. A simplified approach to the anesthesia of porcine laparoscopic surgical subjects. Lab Anim Sci 1993;43:336-7.

28. Cockshott ID, Douglas EJ, Plummer GF, Simons PJ. The pharmacokinetics of propofol in laboratory animals. Xenobiotica 1992;22:369-75.

29. White PF. Propofol: pharmacokinetics and pharmacodynamics. Semin Anesth 1988;7(suppl 1):4-20.

30. Glen JB. Animal studies of the anaesthetic activity of ICI 35868. Br J Anaesth 1980;52:731-42.

Ann Otol Rhinol Laryngol 108:1999

IMAGING CASE STUDY OF THE MONTH

MICROBIAL EXTRACRANIAL ANEURYSM OF THE INTERNAL CAROTID ARTERY: COMPLICATION OF CERVICAL LYMPHADENITIS

TOSHINORI KATO, MD, PHD
MINNEAPOLIS, MINNESOTA

KUMI OTO, MD
TOKYO, JAPAN

TAKASHI ENDO, MD, PHD
TOKYO, JAPAN

JUNICHI FURUSHO, MD, PHD
TOKYO, JAPAN

AKINOBU IWASAKI, MD, PHD
TOKYO, JAPAN

YASUSHI SASAKI, MD, PHD
TOKYO, JAPAN

YOJI IIKURA, MD, PHD
TOKYO, JAPAN

INTRODUCTION

Microbial extracranial aneurysm of the internal carotid artery is extremely rare, and very few cases have been reported in children.[1-7] The causes of infection, such as cervical adenitis, lymphadenitis, peritonsillar abscess, postoperative infection, dental infection, and endocarditis, were reviewed.[1-9] *Staphylococcus* and *Streptococcus* are frequently mentioned as causative organisms.[10] The most common clinical sign is an expanding pulsation of a mass on the neck.[10] However, it is very difficult to diagnose in the early stage, when the pseudoaneurysm is small, because of the lack of signs and symptoms in a small pseudoaneurysm. In a few cases, the rupture of a mass was reported with a large pseudoaneurysm.[8] We describe a pediatric case of a small pseudoaneurysm diagnosed by dynamic magnetic resonance imaging (MRI) in the early stage and describe the clinical course.

CASE REPORT

A 12-year-old boy was admitted to the hospital with a 7-day reported history of right neck burning and pain, and fever of 38.0°C. The swelling of neck lymph nodes and strawberry tongue were observed upon medical examination. The right tonsil presented swelling and slight redness. Laboratory investigations showed elevated peripheral leukocytes of 11.54 × 10^9/L (11,540/mm^3) with 79% polycytes, C-reactive protein of 9.4 mg/dL, and an erythrocyte sedimentation rate of 102 mm/h. The diagnosis of cervical lymphadenitis was made, and treatment with antibiotics was started by intravenous infusion. Pneumonia, endocarditis, and dental and traumatic infections were excluded. Bacterial cultures from the ear, nose, tonsil, and artery were negative.

On the second day of hospitalization, the patient showed an initial intermittent headache. On the seventh day of hospitalization, the body temperature was normal. Laboratory investigations showed peripheral leukocytes of 5.26 × 10^9/L (5,260/mm^3) with 63% polycytes, C-reactive protein of 6.8 mg/dL, and an erythrocyte sedimentation rate of 103 mm/h. The patient's intermittent headache remained.

On the 11th day of hospitalization, the right tonsil was not red, but was shifted. The right side of the neck was not painful or burning. A lymph node swelling was observed, 3 cm in diameter, on the right side of the neck. Laboratory investigations showed C-reactive protein of 2.8 mg/dL.

On the 17th day of hospitalization, as laboratory investigations showed reelevated peripheral leukocytes of 9.09 × 10^9/L (9,090/mm^3) with 70% polycytes, and a C-reactive protein of 4.8 mg/dL, the antibiotic was changed. Headache and neck pain still remained.

On the 20th day of hospitalization, a small mass on the right side of the neck was palpated, but there was not a harsh systolic bruit or tenderness over the mass. An MRI scan was performed for suspected deep neck infection and cerebral vascular diseases. All examinations were performed on a 1.5-T superconducting unit (Signa Advantage GE, USA). Cerebral lesions were excluded. Dynamic MRI scans af-

---

From the Departments of Pediatrics (Kato, Oto, Endo, Furusho, Iwasaki) and Radiology (Sasaki), Showa General Hospital, and the Department of Pediatrics, Showa University School of Medicine (Kato, Furusho, Iikura), Tokyo, Japan, and the Department of Radiology, Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, Minnesota (Kato).

CORRESPONDENCE — Toshinori Kato, MD, PhD, Center for Magnetic Resonance Research, University of Minnesota Medical School, 385 East River Road, Minneapolis, MN 55455.

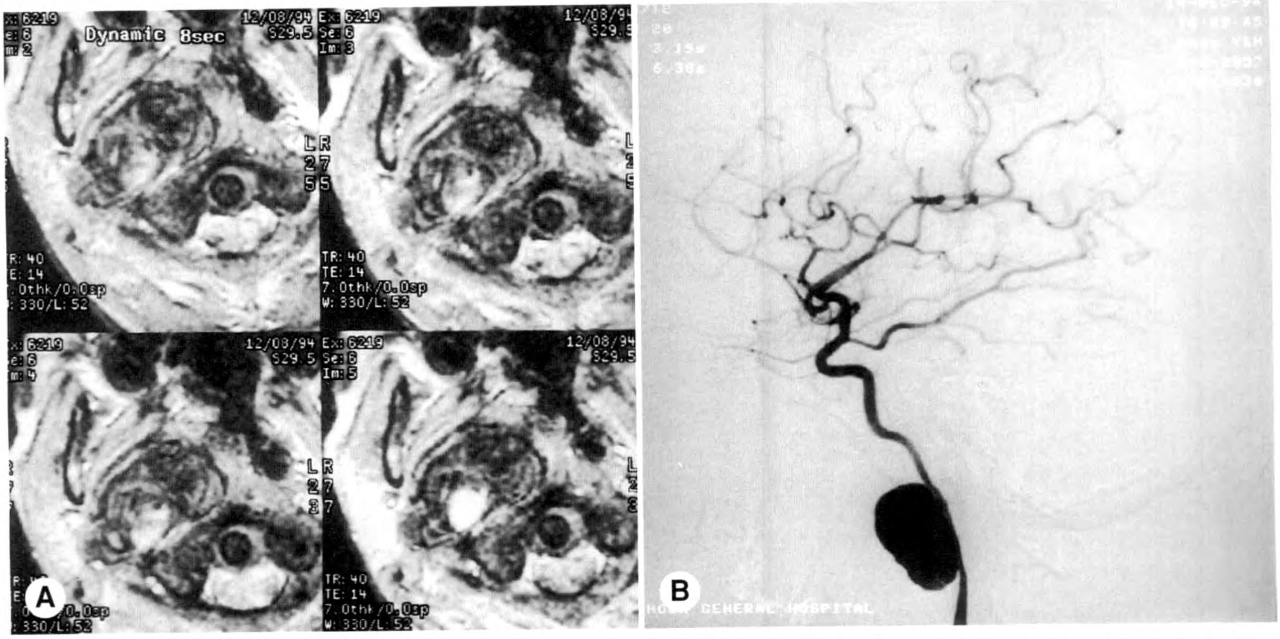


Fig 1. A) Axial dynamic magnetic resonance imaging scans after injection with gadolinium–diethylenetriamine pentaacetic acid confirmed mass to be pseudoaneurysm of internal carotid artery (high-intensity area) and surrounding infected tissues on 20th hospital day. Size of pseudoaneurysm was approximately 1.5 × 1.5 × 1.5 cm^3. B) Selective right internal carotid angiogram from lateral projection on 24th hospital day. Large pseudoaneurysm is at origin of internal carotid artery. Size of pseudoaneurysm was approximately 2.0 × 1.5 × 2.0 cm^3.

ter injection of gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA) confirmed this mass to be a pseudoaneurysm of the internal carotid artery and the surrounding infected tissues on the 20th hospital day (Fig 1A). The size of the pseudoaneurysm was approximately 1.5 × 1.5 × 1.5 cm^3. Laboratory results were improved to peripheral leukocytes of 4.79×10^9/L (4,790/mm^3) with 40% polycytes, a C-reactive protein of 1.0 mg/dL, and an erythrocyte sedimentation rate of 50 mm/h.

On the 24th day of hospitalization, selective internal carotid angiography was performed. A large pseudoaneurysm at the origin of the internal carotid artery was found (Fig 1B). The size of the pseudoaneurysm was approximately 2.0 × 1.5 × 2.0 cm^3.

On the 38th day of hospitalization, a second MRI scan was performed for planning of surgery. An axial MRI scan showed enlargement of the pseudoaneurysm and decreasing space of the surrounding tissues compared with the images taken on the 20th hospital day (Fig 2A). The size of the pseudoaneurysm was approximately 3.0 × 4.0 × 3.0 cm^3. An initial

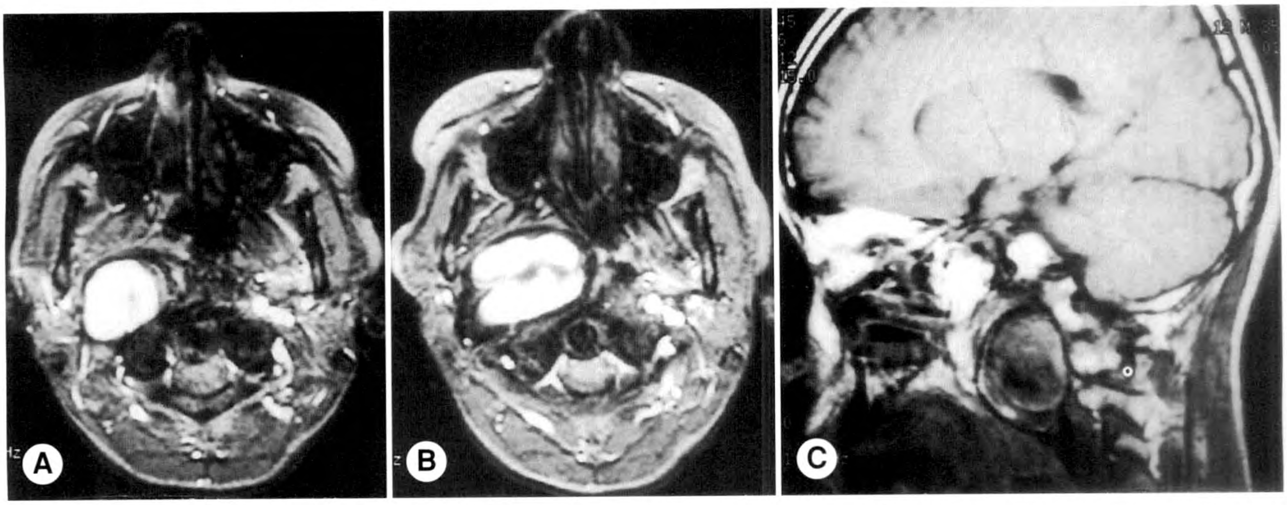


Fig 2. Follow-up magnetic resonance imaging of rapidly growing pseudoaneurysm. A) Axial image showed enlargement of pseudoaneurysm and decreasing space of surrounding tissues on 38th hospital day as compared with 20th hospital day (see Fig 1A). Size of pseudoaneurysm was approximately 3.0 × 4.0 × 3.0 cm^3. B,C) Size of pseudoaneurysm was approximately 5.0 × 5.0 × 5.5 cm^3 on 47th hospital day on B) axial and C) sagittal images.

harsh systolic bruit was heard over the mass. Laboratory investigations implied *Streptococcus* infection, as the antistreptolysin O titer was increased to 6 times over the normal level. The other serologic findings were normal.

On the 47th day of hospitalization, Horner's syndrome was visible on the right side. A follow-up MRI scan was performed. The size of the pseudoaneurysm was approximately $5.0 \times 5.0 \times 5.5$ cm^3 on axial and sagittal MRI (Fig 2B,C).

On the 48th day of hospitalization, an aneurysm ligation and anastomosis with a venous graft between the intracranial internal carotid artery and the extracranial internal carotid artery were performed by surgical operation. Vascular reconstruction was surgically inaccessible for this aneurysm, because the surrounding tissues were severely eroded. The ligation of the pseudoaneurysm succeeded, but the anastomosis was closed after 2 days. The patient's headache and neck pain disappeared after the surgical operation.

After 6 months of surgical treatment, the patient did not present any signs and symptoms of decreased cerebral blood flow in the right hemisphere. Single photon computed tomography performed after injection of acetazolamide (500 mg) revealed lower reactivity to acetazolamide in the right hemisphere (the ligation side) than in the left hemisphere.

DISCUSSION

Unilateral cervical lymphadenitis is a common infection and is mostly bacterial in childhood. However, a microbial extracranial aneurysm of the internal carotid artery is an extremely rare complication of neck infection. Usually, it is difficult to diagnose a small pseudoaneurysm in deep neck space infection with cervical lymphadenitis. Therefore, most cases are diagnosed as large pseudoaneurysms. Before the small mass on the right side of the neck was palpated, the initial symptom in the presented patient was intermittent headache, and the initial sign was a unilaterally enlarged and shifted tonsil. As the pseudoaneurysm could cause a decrease of cerebral blood flow in the ipsilateral cerebral hemisphere, the headache may have been the symptom of a decrease of cerebral blood flow. A mass in the ipsilateral deep neck space may be diagnosed by a unilaterally enlarged and shifted tonsil without redness of the tonsil.

The radiologic diagnosis of the pseudoaneurysm employed echosonography, computed tomography, and angiography. We present the first diagnosis of a pseudoaneurysm by dynamic MRI after injection with Gd-DTPA (0.1 mmol/kg). Dynamic MRI was suitable for the initial diagnostic imaging, allowing for differentiation between the pseudoaneurysm and the surrounding infectious tissues. Angiography was performed for surgical planning purposes and confirmed the obvious lesions of the microbial aneurysm and the previous MRI finding. Echosonography is usually a very convenient procedure for the assessment of deep neck space infection in children, but it is not for surgical planning purposes. After the initial diagnosis of the pseudoaneurysm, unexpected rapid development of the pseudoaneurysm over 4 weeks was detected by serial MRI. We concluded that this rapid growth could not have been monitored by serologic examinations or clinical signs and symptoms such as intermittent headache or a unilaterally enlarged and shifted tonsil. Therefore, serial MRI should be performed for the management of pseudoaneurysm.

Reported treatments of microbial pseudoaneurysms are balloon catheter occlusion,[8] ligation, resection, and reconstruction.[10-12] As several complications were reported after carotid ligation,[11] an anastomosis between the intracranial internal carotid artery and the extracranial internal carotid artery was added to the ligation in our patient. However, the anastomosis joined with the venous graft did not succeed. One of the reasons for the unsuccessful anastomosis may have been the influence of infection still remaining in the surrounding carotid artery. In a patient with a nonmicrobial pseudoaneurysm, an endovascular treatment with coils and stents is a possible choice.[12] As there is more potential for rupture with a microbial pseudoaneurysm, it would be difficult to choose an endovascular reconstruction. In conclusion, we recommend that surgical anastomosis for the supply of the cerebral blood flow should be performed after ligation and elimination of the carotid artery infection.

ACKNOWLEDGMENTS — We thank Joannah O'Hatnick and Emi Kato for their detailed editing, and Tetsuo Ueno, RT, Kazuya Nagata, MD, and Toshiyuki Horiguchi, MD, for their technical and clinical support.

REFERENCES

1. Alexander DW, Leonard JR, Trail ML. Vascular complications of deep neck abscess: a report of four cases. Laryngoscope 1968;78:361-70.

2. Eneroth CM, Tham R. Pseudoaneurysm of the internal carotid artery: a warning of septic erosion. Acta Otolaryngol (Stockh) 1971;72:445-50.

3. Blum DJ, McCaffrey TV. Septic necrosis of the internal carotid artery: a complication of peritonsillar abscess. Otolar-

yngol Head Neck Surg 1983;91:114-8.

4. Sandmann W, Hennerici M, Aulich A, Kniemeyer H, Kremer KW. Progress in carotid artery surgery at the base of the skull. J Vasc Surg 1984;1:734-43.

5. Wells RG, Sty JR. Cervical lymphadenitis complicated by mycotic carotid artery aneurysm. Pediatr Radiol 1991;21: 402-3.

6. Krysl J, Noel de Tilly L, Armstrong D. Pseudoaneurysm of the internal carotid artery: complication of deep neck space infection. AJNR Am J Neuroradiol 1993;14:696-8.

7. Karas DE, Sawin RS, Sie KCY. Pseudoaneurysm of the external carotid artery after tonsillectomy: a rare complication. Arch Otolaryngol Head Neck Surg 1997;123:345-7.

8. Bolender N-F, Bassett MR, Loeser JD, Patterson HC. Mycotic aneurysm of the internal carotid artery. A surgical emergency. Ann Otol Rhinol Laryngol 1984;93:273-6.

9. Stevens HE. Vascular complications of the neck space infection: case report and literature review. J Otolaryngol 1990; 19:206-10.

10. Jebara VA, Acar C, Dervanian P, et al. Mycotic aneurysms of the carotid arteries. Case report and review of the literature. J Vasc Surg 1991;14:215-9.

11. Khalil I, Nawfal G. Mycotic aneurysms of the carotid arteries: ligation vs. reconstruction. Case report and review of the literature. Eur J Vasc Surg 1993;7:588-91.

12. Klein GE, Szolar DH, Raith J, Fruhwirth H, Pascher D, Hausegger KA. Posttraumatic extracranial aneurysm of the internal carotid artery: combined endovascular treatment with coils and stents. AJNR Am J Neuroradiol 1997;18:1261-4.

≈

EAR SURGERY

The 34th Annual Postgraduate Course in Ear Surgery will be held April 5-10, 1999, in Nijmegen, the Netherlands. For information, contact Prof.dr. P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax +31 24 3540251; e-mail J.Cornelisse@kno.azn.nl.

Ann Otol Rhinol Laryngol 108:1999

CLINICOPATHOLOGICAL CONSULTATION

PAPILLARY SQUAMOUS CELL CARCINOMA VERSUS VERRUCOUS SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

ALFIO FERLITO, MD
UDINE, ITALY
ALESSANDRA RINALDO, MD
UDINE, ITALY
KENNETH O. DEVANEY, MD
ANN ARBOR, MICHIGAN
MATHEW J. PUTZI, MD
ANN ARBOR, MICHIGAN

Papillary squamous cell carcinoma and verrucous squamous cell carcinoma of the head and neck may be confused. The clinicopathological profile of the two neoplasms is presented and the differential diagnosis is discussed. A correct diagnosis is imperative in order to institute the most appropriate treatment.

Papillary squamous cell carcinoma (PSCC) and verrucous squamous cell carcinoma (VSCC) pose diagnostic and therapeutic challenges to both pathologists and clinicians. The differential diagnosis between these two tumors is very important, not only for pathological reasons, but also in terms of clinical implications and treatment modalities. In this article we discuss the clinicopathological findings of these tumors.

PAPILLARY SQUAMOUS CELL CARCINOMA

Papillary squamous cell carcinoma is a recently described pathologic entity[1,2]; in the second edition of the World Health Organization (WHO) *Histological Typing of Tumours of the Upper Respiratory Tract and Ear*, published in 1991, the term PSCC has been applied to "invasive squamous cell carcinomas which have an exophytic papillary component."[3(p29)]

This tumor was not classified separately but described under squamous cell carcinoma in the WHO classification,[3] because PSCC had not been categorized as a distinct histopathological type in standard texts or in the periodical literature. Some papers[1,2] have supported classifying PSCC separately like other variants of squamous cell carcinoma. The histopathological and biological characteristics of VSCC, spindle cell carcinoma, adenoid squamous cell carcinoma, basaloid squamous cell carcinoma, and adenosquamous carcinoma are generally recognized as sufficiently different from the conventional squamous cell carcinoma to merit separate classification.[4-7]

Papillary squamous cell carcinoma is a variant of squamous cell carcinoma and may present as either in situ (PSCC in situ or noninvasive PSCC) or invasive tumor (PSCC or invasive PSCC). This tumor occurs most frequently in male patients from 50 to 70 years of age. The most common site is the larynx, followed by the oropharynx and nasopharynx.[1] None of the patients with PSCC had previous recurrent papillomatosis, a lesion correlated with human papillomavirus (HPV) infection, in the series reported by Crissman et al.[1] This does not preclude the development of PSCC in the absence of papillomatosis but in the presence of HPV. There may be several explanations for the absence of HPV: 1) HPV may not be present in the lesion, 2) HPV may be present, but of a different type than those tested for, or 3) HPV may be present, but at concentrations below the sensitivity of the technique.[1] Macroscopically, the tumor appears as an exophytic papillary proliferation.

Microscopically (Fig 1), the lesion is composed of exophytic papillary structures covered by epithelium showing nuclear pleomorphism and atypical mitotic figures containing cores of fibrovascular stroma. Invasion is often present and prominent. In some cases the tumor shows a moderate inflammatory cell reaction in the adjacent connective tissue, which consists of lymphocytes and plasma cells. Some cells of the epithelium have round dark nuclei, surrounded by a marked perinuclear zone or "halo" that appears empty (koilocytosis). Slight surface keratinization may be present, but hyperkeratosis is absent in this

---

From the Department of Otolaryngology–Head and Neck Surgery, University of Udine, Udine, Italy (Ferlito, Rinaldo), and the Department of Pathology, University of Michigan, Ann Arbor, Michigan (Devaney, Putzi).

CORRESPONDENCE — Alfio Ferlito, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Udine, Policlinico Città di Udine, Viale Venezia 410, 33100 Udine, Italy.

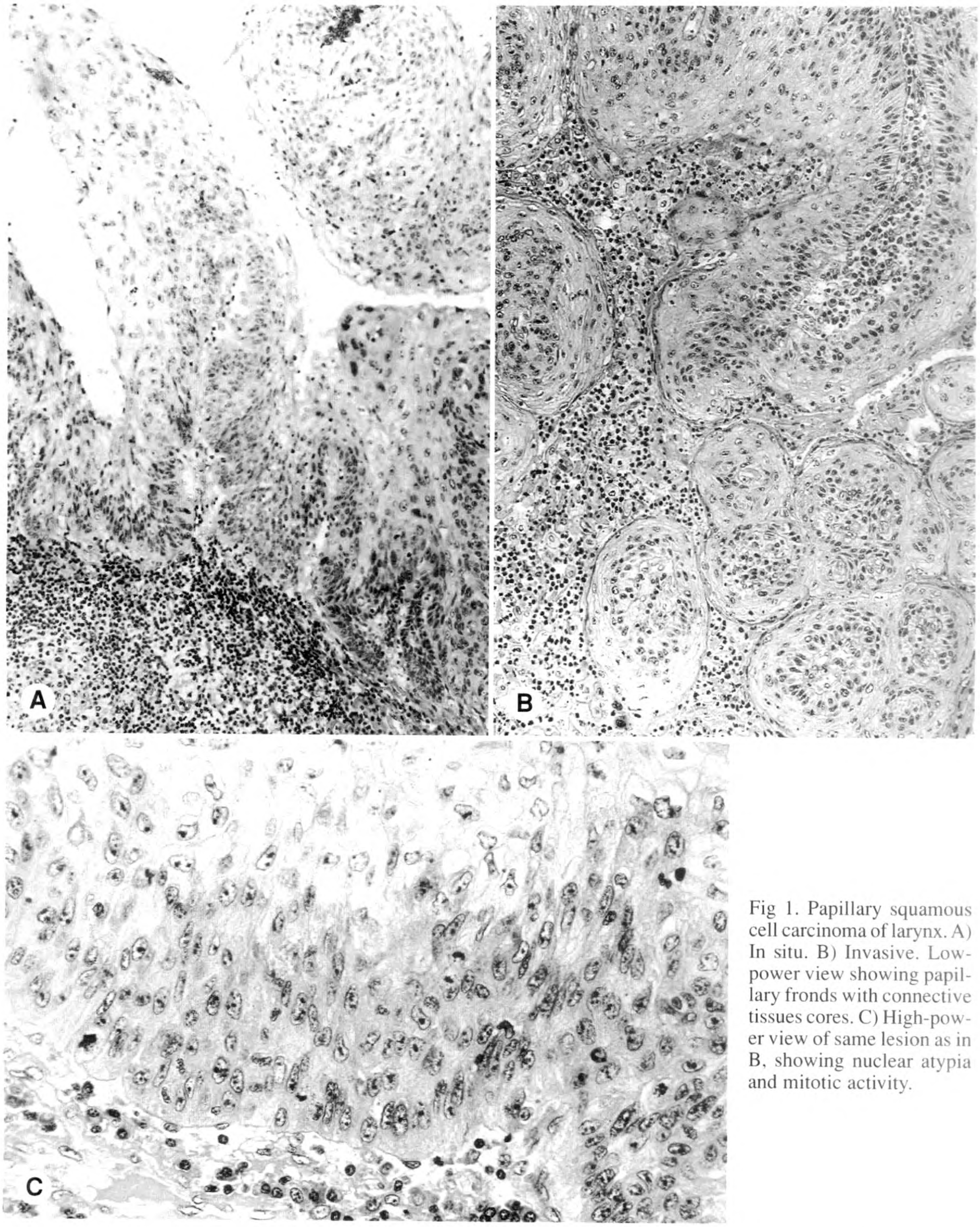


Fig 1. Papillary squamous cell carcinoma of larynx. A) In situ. B) Invasive. Low-power view showing papillary fronds with connective tissues cores. C) High-power view of same lesion as in B, showing nuclear atypia and mitotic activity.

tumor.

VERRUCOUS SQUAMOUS CELL CARCINOMA

Verrucous squamous cell carcinoma is a rare specific clinicopathological entity characterized clinically by a favorable prognosis.[4] This tumor was defined by Ackerman[8] in 1948 as a distinct neoplasm of the oral cavity. He emphasized the predilection of this lesion for the buccal mucosa and lower gingiva. Since then, this neoplasm has been recognized in the mucous membranes of the head and neck, esophagus, skin, genitalia, and urinary bladder. The oral cavity (in particular buccal mucosa, mandibular alveolar ridge, hard and soft palate, oral tongue, lip, alveolar ridge) and the larynx (glottis) are the most common sites. The tumor appears to be associated with tobacco abuse and HPV in some patients. It occurs primarily in men between the ages of 50 and 80 years.

Macroscopically (Fig 2A), the tumor appears to

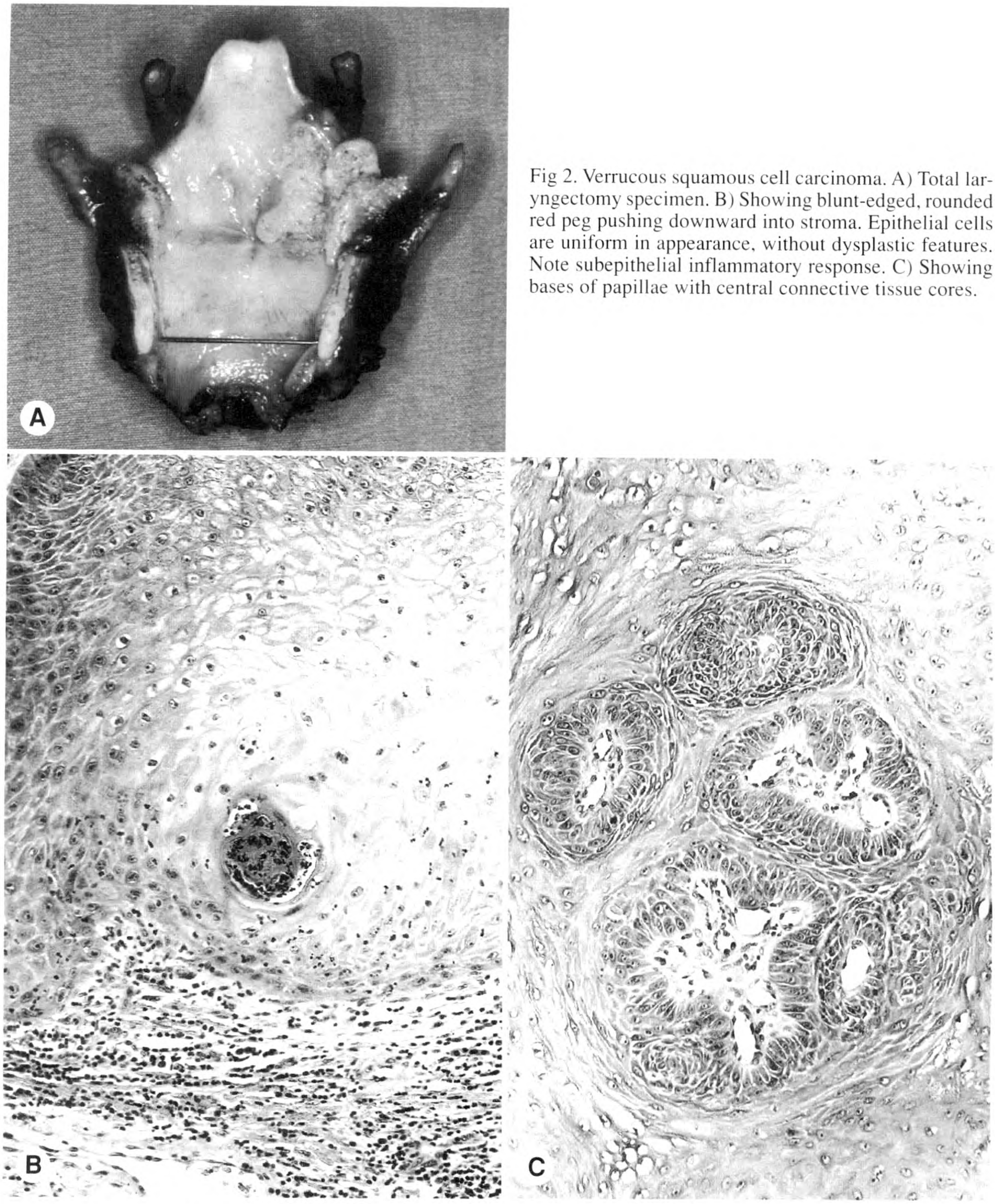


Fig 2. Verrucous squamous cell carcinoma. A) Total laryngectomy specimen. B) Showing blunt-edged, rounded red peg pushing downward into stroma. Epithelial cells are uniform in appearance, without dysplastic features. Note subepithelial inflammatory response. C) Showing bases of papillae with central connective tissue cores.

be a broadly implanted, nonulcerated, exophytic, gray-white fungating mass with papillary fronds and a locally invasive nature. The gross appearance of the lesion is quite characteristic and virtually pathognomonic.[9]

Microscopically (Fig 2B,C), the tumor is composed of islands and solid cords of highly differentiated squamous epithelial cells. Cytological malignancy criteria are lacking or minimal. Anaplasia is absent, and its absence may lead to an incorrect diagnosis. Prominent koilocytotic cells with dark pyknotic nuclei have occasionally been observed. The surface is covered with a thick layer of keratinized cells arranged in invaginating bulbous acanthotic folds. Vertical sections of the neoplasm show epithelial spires capped by a thick parakeratotic or keratotic layer. The continuity of the irregular verrucous surface is maintained by long filiform processes of well-differentiated squamous cells. There is typically a considerable inflammatory reaction in the stroma composed of lymphocytes, plasma cells, and histiocytes that tend to delimit the tumor mass, the margins of which appear to be pushing and blunt rather

COMPARISON OF PAPILLARY SQUAMOUS CELL CARCINOMA AND VERRUCOUS SQUAMOUS CELL CARCINOMA IN TERMS OF PATHOLOGICAL AND CLINICAL FINDINGS

	Papillary	*Verrucous*
Macroscopic appearance	Exophytic, papillary	Fungating, cauliflower-like tumor
Most common sites	Larynx, oral cavity	Oral cavity, larynx
Incidence	<0.1%	2%-4%
Cellular differentiation	Moderate	High
Cytological features of malignancy	Present	Absent or occasional
Margins	Infiltrating	Pushing
Cellular response	Moderate	Prominent
Cleftlike spaces and small cysts	Absent	Present
Microabscesses	Absent	Usually present
Grade of malignancy	Moderate	Low
Surface keratinization	Slight to minimal	Marked ("church-spire" keratosis)
Nuclear pleomorphism	Present	Absent
Granulomatous reaction in stroma	Absent	Present
Hyperchromatism	Present	Absent
Koilocytic changes	Present	Present
Invasion	Present	Very limited
Regional metastases	May be present	Absent
Cervical adenopathy	Represents metastatic disease	Represents reactive changes
Distant metastases	Rare	Absent
Aggression	Variable	Low
Prognosis	Good	Excellent
Prophylactic neck dissection	Is indicated in stage T3 or greater	Is not indicated

than infiltrating. Epithelial pearls, multisized cystic inclusions of laminated keratin, and microabscesses and macroabscesses may be visible. Stromal foreign body reaction to keratin material can also be seen, close to epithelial pearls or surrounding keratinized matter. Mitoses are rare and tend to be concentrated in the basal-parabasal region; benign cellular features, coupled with the orderly maturation sequence, belie the locally destructive nature of the tumor. Invasion of the basement membrane and glandular structures is often apparent, and if the tumor is neglected, there may be destruction of adjoining tissues, including muscle, cartilage, and bone.[10] Accumulation of p53 protein is frequently observed, suggesting possible mutations of this gene in the tumor.[11] Overexpression of cyclin D1 has been observed, but no alterations of Rb staining; these findings suggest that Rb may be functionally inactivated by overexpression of cyclin D1 or HPV infection.[11]

Verrucous squamous cell carcinoma does not metastasize, but may be associated with benign lymph node enlargements secondary to the inflammatory reaction related to the carcinoma.[12]

At present, VSCC is recognized by pathologists and clinicians as a clinicopathological entity. The tumor shows certain unique features of clinical significance. It does not manifest a capacity for cervical and distant metastases, but it is locally invasive and destructive. The tumor has a propensity for local recurrence after irradiation.[13]

DISCUSSION

Clinically, both lesions (PSCC and VSCC) appear as an exophytic, papillary tumor, but the latter is a white, warty, fungating tumor with multiple filiform-like projections. Careful histopathological investigations are needed to establish the correct diagnosis, which is essential for appropriate treatment. Differential diagnosis between PSCC and VSCC can be very challenging. Adequate biopsy including a good epithelial-stromal interface is ideal for diagnosing VSCC. A full-thickness biopsy is crucial to allow a definitive histologic diagnosis of PSCC.[2]

A tumor that shows atypia on biopsy is probably not a VSCC, but a well-differentiated PSCC.[2] Sometimes the pathologist uses the ambiguous expression "squamous cell carcinoma with verrucous appearance," but histological reexamination of these tumors usually supports a diagnosis of squamous cell carcinoma (conventional or papillary type). Verrucous squamous cell carcinomas containing areas that are indistinguishable from conventional squamous cell carcinoma have been reported in the literature.[14,15] Such tumors are called hybrid carcinomas, and they are more aggressive than VSCC. Ishiyama et al[2] suggest that these hybrid tumors are probably identical to PSCC.

Verrucous squamous cell carcinoma is distinguishable from PSCC by its lack of cytological features of malignancy; a high degree of cellular differentiation; marked surface keratinization; the presence of advancing, pushing, and well-demarcated margins; the presence of cleftlike spaces, small cysts, and microabscesses; evidence of foreign body granulomas near epithelial pearls of keratinized matter; prominent stromal evidence of a chronic reaction; and the absence of lymph node or visceral metastases.[9] The Table lists the different clinicopathological properties of PSCC and VSCC.

A correct diagnosis is imperative in order to institute the most appropriate treatment. Surgical complete excision of the primary lesion is the treatment of choice for PSCC. Ishiyama et al[2] believe that patients with lesions of stage T3 or greater should undergo a prophylactic neck dissection, in consideration of the high rate of neck metastasis. Most squamous malignancies with papillary components are thought to behave similarly to invasive squamous carcinoma.[1]

The treatment of choice for VSCC is excision by laser or conservative surgical resection when possible,[16] without neck dissection,[5] even though enlarged lymph nodes may be palpated.[4] The prognosis is excellent even when the lesion is very large, provided that adequate treatment is adopted from the beginning.[17]

REFERENCES

1. Crissman JD, Kessis T, Shah KV, et al. Squamous papillary neoplasia of the adult upper aerodigestive tract. Hum Pathol 1988;19:1387-96.

2. Ishiyama A, Eversole LR, Ross DA, et al. Papillary squamous neoplasms of the head and neck. Laryngoscope 1994;104:1446-52.

3. World Health Organization. Histological typing of tumours of the upper respiratory tract and ear. 2nd ed. Berlin, Germany: Springer-Verlag, 1991.

4. Ferlito A, Recher G. Ackerman's tumor (or verrucous carcinoma) of the larynx. A clinicopathological study of 77 cases. Cancer 1980;46:1617-30.

5. Ferlito A, Devaney KO, Rinaldo A. Squamous neoplastic component in unconventional squamous cell carcinomas of the larynx. Ann Otol Rhinol Laryngol 1996;105:926-32.

6. Barnes L, Ferlito A, Altavilla G, MacMillan C, Rinaldo A, Doglioni C. Basaloid squamous cell carcinoma of the head and neck: clinicopathological features and differential diagnosis. Ann Otol Rhinol Laryngol 1996;105:75-82.

7. Ferlito A, Devaney KO, Rinaldo A, Milroy CM, Carbone A. Mucosal adenoid squamous cell carcinoma of the head and neck. Ann Otol Rhinol Laryngol 1996;105:409-13.

8. Ackerman LV. Verrucous carcinoma of the oral cavity. Surgery 1948;23:670-8.

9. Ferlito A. Unusual forms of squamous carcinoma. In: Ferlito A, ed. Surgical pathology of laryngeal neoplasms. London, England: Chapman and Hall, 1996:143-71.

10. Ferlito A. Diagnosis and treatment of verrucous squamous cell carcinoma of the larynx: a critical review. Ann Otol Rhinol Laryngol 1985;94:575-9.

11. Gimenez-Conti IB, Collet AM, Lanfranchi H, et al. p53, Rb, and cyclin D1 expression in human oral verrucous carcinomas. Cancer 1996;78:17-23.

12. Friedmann I, Ferlito A. Granulomas and neoplasms of the larynx. Edinburgh, Scotland: Churchill Livingstone, 1996:167-85.

13. Ferlito A, Rinaldo A, Mannarà GM. Is primary radiotherapy an appropriate option for the treatment of verrucous carcinoma of the head and neck? J Laryngol Otol 1998;112:132-9.

14. Batsakis JG, Hybels R, Crissman JD, Rice DH. The pathology of head and neck tumours: verrucous carcinoma, part 15. Head Neck Surg 1982;5:29-38.

15. Medina JE, Dichtel MW, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathological study of 104 cases. Arch Otolaryngol 1984;110:437-40.

16. McCaffrey TV, Witte M, Ferguson MT. Verrucous carcinoma of the larynx. Ann Otol Rhinol Laryngol 1998;107:391-5.

17. Orvidas LJ, Olsen KD, Lewis JE, Suman VJ. Verrucous carcinoma of the larynx: a review of 53 patients. Head Neck 1998;20:197-203.

EDITORIAL

WHAT IS "SPONTANEOUS" CEREBROSPINAL FLUID RHINORRHEA?

CLASSIFICATION OF CEREBROSPINAL FLUID LEAKS

GADY HAR-EL, MD
BROOKLYN, NEW YORK

Since the first descriptions of nontraumatic cerebrospinal fluid (CSF) leaks of the temporal bone (in the French literature in 1897[1]) and via the nasal passages (in the British literature in 1899[2]), the term "spontaneous CSF leak" has been used extensively in the literature. However, there is a certain degree of confusion concerning CSF leaks when a traumatic cause is not apparent. Careful review of the literature reveals that the term "spontaneous" is given different meanings by different authors. Many authors divide CSF leaks into traumatic (surgical or nonsurgical) and spontaneous, and therefore consider a spontaneous CSF leak the same as a nontraumatic one.[3-10] Others define a spontaneous leak as one not related to trauma, surgery, or *neoplasm.*[11] According to Lundy et al,[12] a spontaneous CSF leak is one that is not related to infection, trauma, or tumor.

May et al[13] consider a CSF leak to be spontaneous if no history of trauma or *congenital defect* can be elicited. Pappas et al[14,15] define a spontaneous CSF leak as one without a history of trauma, congenital defect, or *infection.* Other definitions state that "spontaneous CSF leakage occurs without *apparent* cause"[14]; for some of us, in daily practice, a spontaneous CSF leak is defined as one without a *recent* cause.

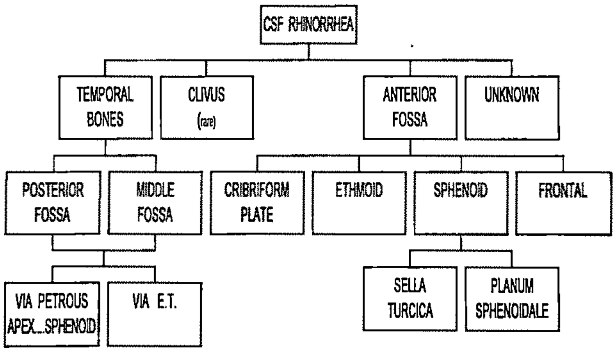


Fig 1. Classification of cerebrospinal fluid (CSF) rhinorrhea according to site of leak. E.T. — eustachian tube.

O'Connell,[16] in 1964, subdivided spontaneous CSF leaks into "primary spontaneous" or "idiopathic" leaks, in which a precipitating cause could not be found, and "secondary spontaneous" leaks, in which a cause was eventually discovered. Ommaya et al,[17] in 1968, proposed a classification of CSF rhinorrhea that avoids the use of the term "spontaneous." The main division they used was that between traumatic and nontraumatic leaks. They stated that we should avoid using the term "primary spontaneous" as a wastebasket for those cases in which the true cause has not been discovered, and that we should avoid the use of "secondary spontaneous" because it is a logically impossible phrase.

Webster's dictionary defines "spontaneous" as "developing without apparent external influence or force or from some undiscoverable cause."[18] Since a careful history and physical, radiological, endoscopic, and surgical examinations usually result in information that will make most patients ineligible for the Webster's dictionary definition, actual cases that fit such a definition are extremely rare.

Cerebrospinal fluid rhinorrhea may be classified according to location or according to the known or

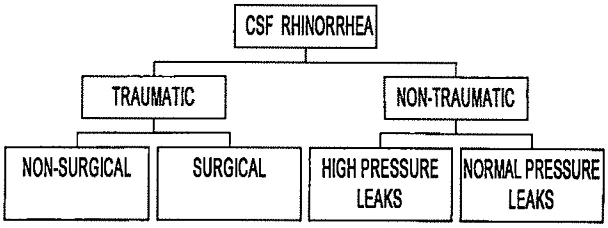


Fig 2. Classification of CSF rhinorrhea according to cause.

From the Departments of Otolaryngology and Neurosurgery, State University of New York Health Science Center at Brooklyn, Brooklyn, New York.

Presented in part at the meeting of the American Rhinologic Society, Scottsdale, Arizona, May 11, 1997.

CORRESPONDENCE — Gady Har-El, MD, SUNY-HSCB, Dept of Otolaryngology, Box 126, 450 Clarkson Ave, Brooklyn, NY 11203.

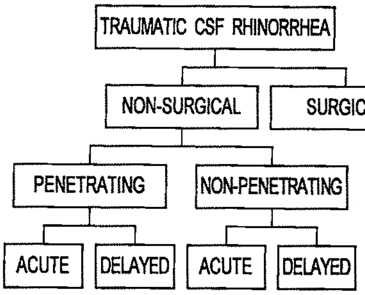


Fig 3. Classification of traumatic CSF rhinorrhea.

presumed cause. Every communication regarding CSF rhinorrhea should include the site as well as the cause. Knowledge of the site of the leak can certainly help with identification of the cause and vice versa. Classification of CSF rhinorrhea according to the site of the leak is presented in Fig 1. It should be noted that in addition to the eustachian tube route, there are rare cases of CSF leaks originating in the temporal bone and traveling through the petrous apex and via the sphenoid sinus into the nose. The communication between the petrous apex and the sphenoid sinus may be caused by variance of normal anatomy (extensive lateral pneumatization of the sphenoid sinus and/or extensive medial pneumatization of the petrous bone) or be secondary to a pathological process such as a fracture or an erosive tumor.

Classification of CSF rhinorrhea by cause begins with the main division into traumatic and nontraumatic leaks (Fig 2). Traumatic leaks are divided into surgical (or iatrogenic) and nonsurgical.[5] Nonsurgical leaks are further subdivided into penetrating and nonpenetrating (Fig 3). Both entities may present as an acute leak at the time of trauma or as a delayed one. It is the delayed presentation of traumatic CSF rhinorrhea that may initially be given the diagnosis of spontaneous leak.[3,19-21] However, it is our experience that a very careful and detailed history may identify related head trauma in the past. High-resolution computed tomography may identify a fracture line, and during surgical exploration, a fracture line may be seen. We believe that the term "spontaneous" should not be used in these cases. Salca and Danaila[20] presented a case of CSF rhinorrhea occurring 27 years after head injury. Surgical exploration revealed a linear fracture of the cribriform plate. Crawford et al[21] presented a case of CSF rhinorrhea and meningitis occurring 37 years after head injury.

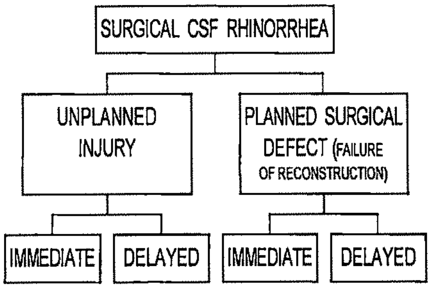


Fig 4. Classification of surgical CSF rhinorrhea.

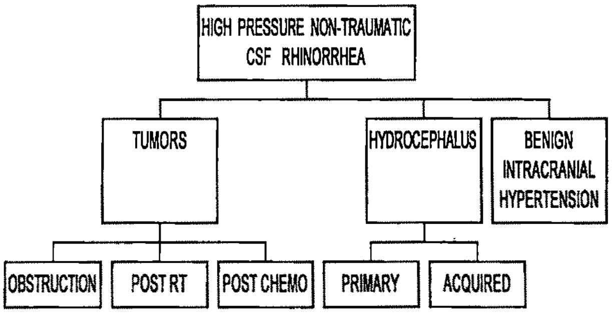

HIGH PRESSURE NON-TRAUMATIC CSF RHINORRHEA
TUMORS
HYDROCEPHALUS
BENIGN INTRACRANIAL HYPERTENSION
OBSTRUCTION
POST RT
POST CHEMO
PRIMARY
ACQUIRED

Fig 5. Classification of high-pressure nontraumatic CSF rhinorrhea. RT — radiotherapy; chemo — chemotherapy.

In the group of surgical CSF rhinorrhea (Fig 4), we differentiate between unplanned injury (eg, complication of ethmoidectomy) and planned dural defects in which the reconstructive component of the procedure may have failed (eg, acoustic neuroma resection).

Nontraumatic CSF rhinorrhea is subdivided into high-pressure and low-pressure leaks[5,6,17] (Fig 2). The classification of high-pressure nontraumatic CSF rhinorrhea is presented in Fig 5. Although some of these patients may present to the rhinologist, once a diagnosis is made, they will most commonly require neurosurgical treatment.[22] However, in the case of benign intracranial hypertension (pseudotumor cerebri), diagnosis may require close cooperation between the rhinologist, neurologist, and neurosurgeon.[23] Before the repair, the primary pathologic process should be addressed, because persistent high intracranial pressure may result in failure of the repair procedure.[23-25]

Classification of normal-pressure, nontraumatic CSF rhinorrhea is presented in Fig 6.[12,17,26] Subclassification of the congenital and idiopathic subgroups is presented in Fig 7. It should be noted that tumors appear in both the high-pressure and normal-pres-

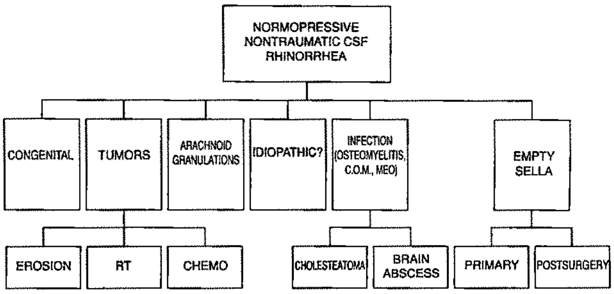


Fig 6. Classification[12,17,26] of normal-pressure nontraumatic CSF rhinorrhea. C.O.M. — chronic otitis media; MEO — "malignant" external otitis.

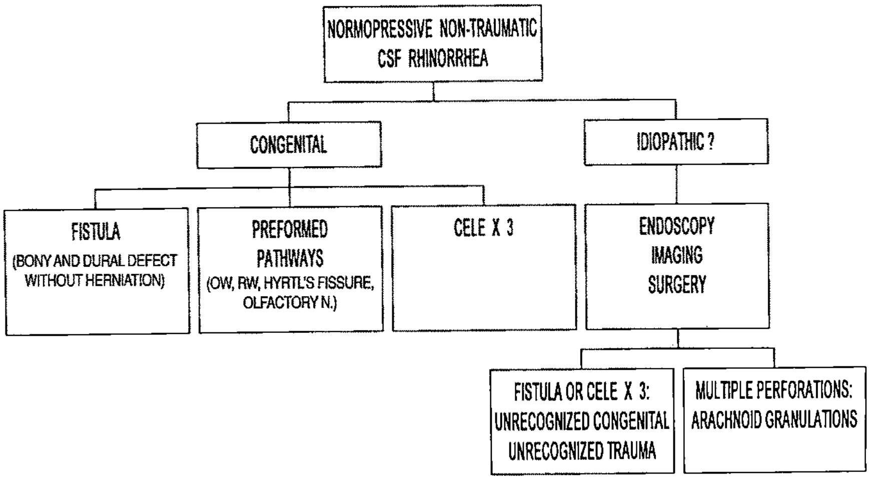

NORMOPRESSIVE NON-TRAUMATIC CSF RHINORRHEA
CONGENITAL
IDIOPATHIC ?
FISTULA (BONY AND DURAL DEFECT WITHOUT HERNIATION)
PREFORMED PATHWAYS (OW, RW, HYRTL'S FISSURE, OLFACTORY N.)
CELE X 3
ENDOSCOPY IMAGING SURGERY
FISTULA OR CELE X 3: UNRECOGNIZED CONGENITAL UNRECOGNIZED TRAUMA
MULTIPLE PERFORATIONS: ARACHNOID GRANULATIONS

Fig 7. Further subclassification of congenital and idiopathic CSF rhinorrhea. OW — oval window; RW — round window; N. — nerve; CELE × 3 — meningocele, encephalocele, or meningoencephalocele.

sure groups (Figs 5 and 6). In the high-pressure group, tumors may result in CSF leaks because of obstruction or because of edema following treatment, both of which may lead to increased intracranial pressure.[5,6,25] In the normal-pressure group, tumors may have a direct erosive effect on the skull base and dura resulting in a leak,[5] and treatment modalities such as irradiation and chemotherapy may result in bone necrosis leading to a CSF leak.

If "spontaneous" CSF leaks do exist, they belong to the group of "idiopathic" or "unknown origin" CSF rhinorrhea. However, as stated above, careful history combined with endoscopic, radiologic, and surgical examination will commonly result in the identification of a probable cause of the leak.[3] Therefore, most of these "idiopathic" cases will eventually have a more specific diagnosis. True "idiopathic" CSF rhinorrhea is extremely rare. According to Ommaya et al,[17] it does not really exist.

Two additional entities should be mentioned, as they may explain some of the "idiopathic" leaks. Ommaya et al[17] suggested that their "focal atrophy" theory may explain idiopathic as well as congenital leaks. According to this theory, atrophy of the normal contents at the cribriform plate or sella turcica areas, which may be secondary to ischemia, results in reduced soft tissue bulk. The empty space thus created leads to the formation of an arachnoidal pouch that is filled with CSF. The pouch with its pulsating CSF exerts a local erosive effect on the bony skull base. This will eventually result in a bony defect leading to a fistula, meningocele, or meningoencephalocele herniating extracranially. The end result is a CSF leak. This theory lacks reliable anatomic studies to support it.

Arachnoid granulations have been proposed as a mechanism of CSF leaks of unknown origin.[4,27-29] In contrast to the focal atrophy theory, this entity received significant attention and discussion, especially in the otologic literature, and is supported by anatomic studies.[4,27]

Arachnoid granulations are normal microstructures that provide the primary mechanism for CSF resorption into the intracranial venous system. The majority of arachnoid granulations are located along the superior sagittal sinus and its tributaries. However, they may be also found in the skull base. Anatomic studies identified the structures in both the middle fossa and posterior fossa surfaces of the temporal bone, as well as the roof of the ethmoid and sphenoid sinuses. According to Gacek,[4] since skull base arachnoid granulations do not extend into a venous sinus lumen, they are not covered by endothelium, but by dural extension. This creates a closed system of CSF within the arachnoid granulation that transmits pulsations through its capsule to cause destruction of the surrounding bone.[30] This theory may explain idiopathic CSF leaks. Anatomic studies by Gacek[4] and by Schuknecht and Gulya[27] support this theory.

CONCLUSION

What is "spontaneous" CSF rhinorrhea? Careful review of the literature certainly does not provide an answer. This term is given different meanings by different authors. Until a consensus on the definition of spontaneous CSF leak is reached by rhinologists, otologists, neurosurgeons, and skull base surgeons, we prefer not to use this term at all. Any communication regarding CSF leaks should include specific information on the site of the leak and the known or presumed cause. Careful history-taking and endoscopic, radiologic, and surgical findings will result in the identification of the cause in most cases. For the rare cases in which no cause can be identified, the term "idiopathic" (or "of unknown origin") seems appropriate.

ACKNOWLEDGMENTS — The author thanks Drs Frank E. Lucente, Neil M. Sperling, and Michael Ehrenhaus for their assistance.

REFERENCES

1. Escat E. Ecoulement spontane de liquide cephalorachidien par le conduit auditif externe, fistule congenitale probable. Arch Int Laryngol 1897;10:653-9.

2. Thomson StC. The cerebrospinal fluid: its spontaneous escape from the nose. London: Cassell, 1899.

3. Hubbard JL, McDonald TJ, Pearson BW, Laws ER. Spontaneous cerebrospinal fluid rhinorrhea; evolving concepts in diagnosis and surgical management based on the Mayo Clinic experience from 1970 through 1981. Neurosurgery 1985;16: 314-21.

4. Gacek RR. Arachnoid granulation cerebrospinal fluid otorrhea. Ann Otol Rhinol Laryngol 1990;99:854-62.

5. Zlab MK, Moore GF, Daly DT, Yonkers AJ. Cerebrospinal fluid rhinorrhea: a review of the literature. Ear Nose Throat J 1992;71:314-7.

6. Colquhoun IR. CT cisternography in the investigation of cerebrospinal fluid rhinorrhea. Clin Radiol 1993;47:403-8.

7. Hughes RGM, Jones NS, Robertson IJA. The endoscopic treatment of cerebrospinal fluid rhinorrhea: the Nottingham experience. J Laryngol Otol 1997;111:125-8.

8. Burns JA, Dodson EE, Gross CW. Transnasal endoscopic repair of cranionasal fistulae: a refined technique with long-term follow-up. Laryngoscope 1996;106:1080-3.

9. Lanza DC, O'Brien DA, Kennedy DW. Endoscopic repair of cerebrospinal fluid fistulae and encephaloceles. Laryngoscope 1996;106:1119-25.

10. Murata Y, Yamada I, Isotani E, Suzuki S. MRI in spontaneous cerebrospinal fluid rhinorrhea. Neuroradiology 1995;37: 453-5.

11. Pribram HFW, Hass AC, Nishioka H. Radiographic localization of a spontaneous cerebrospinal fluid fistula. J Neurosurg 1996;24:1031-3.

12. Lundy LB, Graham MD, Kartush JM, LaRouere MJ. Temporal bone encephalocele and cerebrospinal fluid leaks. Am J Otol 1996;17:461-9.

13. May JS, Mikus JL, Matthews BL, Browne JD. Spontaneous cerebrospinal fluid. Am J Otol 1995;16:765-71.

14. Pappas DG, Hoffman RA, Cohen NL, Pappas DG. Spontaneous temporal bone cerebrospinal fluid leak. Am J Otol 1992; 13:534-9.

15. Pappas DG, Pappas DG, Hoffman RA, Harris SD. Spontaneous cerebrospinal fluid leaks originating from multiple skull base defects. Skull Base Surg 1996;6:227-30.

16. O'Connell JEA. Primary spontaneous cerebrospinal fluid rhinorrhea. J Neurol Neurosurg Psychiatry 1964;27:241-6.

17. Ommaya AK, Di Chiro G, Baldwin M, Pennybacker JB. Non-traumatic cerebrospinal fluid rhinorrhea. J Neurol Neurosurg Psychiatry 1968;31:214-25.

18. Gove PB, ed. Webster's third new international dictionary. Springfield, Ill: Merriam-Webster, 1986:2204.

19. Schick B, Draf W, Kahle G, Weber R, Wallenfang T. Occult malformations of the skull base. Arch Otolaryngol Head Neck Surg 1997;123:77-80.

20. Salca HC, Danaila L. Onset of uncomplicated cerebrospinal fluid fistula 27 years after head injury. Surg Neurol 1997; 47:132-3.

21. Crawford C, Kennedy N, Weir WR. Cerebrospinal fluid rhinorrhea and *Hemophilus influenzae* meningitis 37 years after a head injury. J Infect 1994;28:93-7.

22. Rovit RL, Shechter MM, Nelson K. Spontaneous "high-pressure cerebrospinal rhinorrhea" due to lesions obstructing flow of cerebrospinal fluid. J Neurosurg 1969;30:406-12.

23. Clark D, Bullock P, Hui T, Firth J. Benign intracranial hypertension: a cause of CSF rhinorrhea. J Neurol Neurosurg Psychiatry 1994;57:847-9.

24. Friedman M, Venkatesan TK, Caldarelli DD. Composite mucochondral flap for repair of cerebrospinal fluid leaks. Head Neck 1995;17:414-8.

25. Bhayani R, Bafna P, Goel A. Cerebrospinal fluid rhinorrhea: unusual presentation of acoustic neurinoma. Br J Neurosurg 1993;7:705-7.

26. Melamed J, Stone B, Beucher WN. Spontaneous cerebrospinal fluid rhinorrhea with associated sinusitis and allergic rhinitis. Allergy Proc 1994;15:197-200.

27. Schuknecht HF, Gulya AJ. Anatomy of the temporal bone with surgical implications. Philadelphia, Pa: Lea and Febiger, 1986:125-6.

28. Kaufman B, Nulsen FE, Weiss MH, et al. Acquired spontaneous, nontraumatic normal pressure cerebrospinal fluid fistula originating from the middle fossa. Neuroradiology 1977; 122:379-87.

29. Yerkes SA, Thompson DH, Fisher WS. Spontaneous cerebrospinal fluid rhinorrhea. Ear Nose Throat J 1992;71:318-20.

30. Coiteiro D, Tavora L, Antunes JL. Spontaneous cerebrospinal fluid fistula through the clivus: report of two cases. Neurosurgery 1995;37:826-8.

EDITOR'S NOTE – Editorials are invited from time to time on topics that are controversial, when new landmarks are identified, or terminologic modifications appear to be in order. Communications from readers are welcome.

BRIAN F. MCCABE

Ann Otol Rhinol Laryngol 108:1999

INTEGRITY OF THE AUDITORY PATHWAY IN YOUNG CHILDREN WITH CONGENITAL AND POSTMENINGITIC DEAFNESS

THOMAS P. NIKOLOPOULOS, PHD
GERARD M. O'DONOGHUE, MCH, FRCS
STEVE M. MASON, PHD
KEVIN P. GIBBIN, FRCS
NOTTINGHAM, ENGLAND

This study compares the functional integrity of the auditory pathways of congenitally deaf and postmeningitically deaf children. We used the electrical auditory brain stem response evoked by promontory stimulation to assess 49 profoundly deaf children before cochlear implantation. The age at implantation ranged from 21 months to 15 years (mean 4.5 years). The onset of deafness was either congenital or up to the age of 2 years (mean 5 months). The cause of deafness was meningitis in 19 children (39%) and congenital in 30 (61%). The number of children with identifiable waveform components (eV, eIII, and eII) was significantly greater in the congenitally deaf group. We also analyzed the amplitudes, the latencies, and 4 parameters of the amplitude input-output functions. All the statistically significant differences were in favor of better responses in the congenitally deaf children. These results suggest that the functional status of the peripheral neurons of the auditory pathways may be more intact in congenitally deaf children than in postmeningitic children.

KEY WORDS — children, cochlear implant, congenital deafness, deafness, electrical auditory brain stem response, input-output function, meningitis, promontory test, slope.

INTRODUCTION

It has become apparent that children with profound hearing loss, who receive little or no benefit from hearing aids, can derive benefit from a cochlear implant.[1,2] The prevalent view regarding the cause of deafness, based mainly on the findings of Staller et al,[1] has been that implanted postmeningitically deaf children would outperform congenitally deaf children due to their having some period of auditory experience. However, studies have debated this view and claimed that congenitally deaf children have the potential to derive as much, or even better, benefit from a cochlear implant as do children with acquired prelingual deafness.[3-5] This argument is based on the assumption that the auditory pathways in congenitally deaf children have at least the same, or even better, functional status as those in postmeningitic children.

The aim of this study was to further investigate the latter hypothesis by using the electrical auditory brain stem response evoked by promontory stimulation (Prom-EABR) to compare the integrity of the auditory pathways in children deafened after meningitis and in congenitally deaf children.

MATERIALS AND METHODS

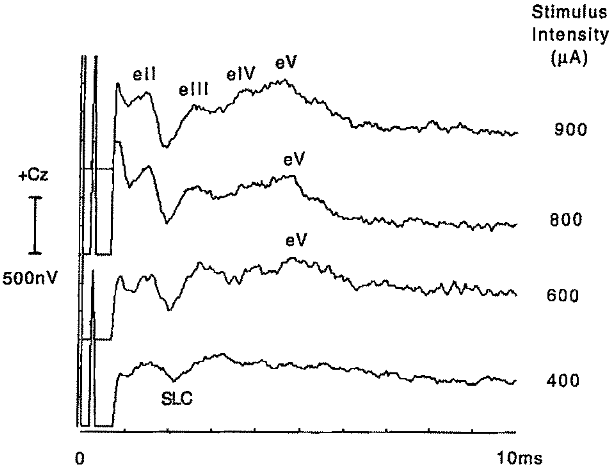
We evaluated 49 children (98 ears) with ages at implantation ranging from 21 months to 15 years (mean 4.5 years). The onset of deafness was either congenital or up to the age of 2 years (mean 5 months). The preoperative auditory deprivation ranged from 3 months to 15 years (mean 4 years). The cause of deafness was meningitis in 19 children (39%) and congenital in 30 (61%). Recordings of the Prom-EABR were carried out at the time of surgery, after the child was anesthetized and before implantation.[6] The outcome of the test on each ear was used to assist selection of the ear for implantation, also taking into consideration other factors such as the results from imaging and any preoperative residual hearing. Several reports suggest that the Prom-EABR (mainly the amplitudes and the input-output function) has the ability to predict survival of auditory neurons.[7-10]

A detailed account of the recording procedure for the Prom-EABR has been described previously.[6] A biphasic electrical pulse stimulus with constant current output and a repetition rate of 85 pulses per second was presented to the promontory in the middle ear, via a transtympanic needle electrode. A large carbon pad electrode was positioned on the ipsilateral mastoid for the return current. The duration of each phase of the biphasic pulse was 400 microseconds, and the onset phase was alternately inverted within the train of pulses.

The maximum amplitude available from the stimu-

From the ENT & Audiology Directorate (Nikolopoulos, O'Donoghue, Gibbin), and the Department of Medical Physics (Mason), Queen's Medical Centre, Nottingham University Hospital, Nottingham, England.

CORRESPONDENCE — Steve M. Mason, PhD, Dept of Medical Physics, Queen's Medical Centre, Nottingham University Hospital, Nottingham NG7 2UH, England.



Typical intensity series of promontory electrical auditory brain stem response waveforms, showing waves eV, eIII, and eII and short latency component (SLC).

lator was 1,000 µA. The voltage of the output pulse was monitored on a battery-powered oscilloscope in order to check that the contact impedance of the promontory stimulating needle was sufficiently low to achieve the expected current output. The patient was under the influence of muscle relaxant in order to eliminate any possible contamination of the responses with evoked myogenic activity.

Data collection was carried out on a Medelec Mistral evoked potential system. Scalp recording electrodes were positioned at the vertex and contralateral mastoid with a ground electrode on the forehead. The on-line signal was recorded with a filter bandwidth of 1 Hz to 3,000 Hz. Averaged waveforms were collected with a 10-millisecond (ms) poststimulus epoch and 2,048 individual sweeps.

The Prom-EABR was recorded in steps of 100 µA from threshold levels up to the maximum 1,000 µA available. If the response waveform was absent or poorly defined, the stimulating needle electrode was repositioned. The amplitude of the individual wave of the response was measured from the peak component to the following negative trough.

The amplitude input-output (I/O) function of the Prom-EABR was measured with 4 parameters (slope, maximal slope, relative growth rate, and maximal relative growth rate) for waves eV, eIII, and eII. The methods of calculation of these parameters have been described in detail elsewhere.[11] We evaluated the slopes and growth rates using only the suprathreshold data points (not including the zero values), and we considered any negative slopes or growth rates as having zero value. Measurements of amplitudes of less than 25 nV were considered to be zero, being within the noise floor. Cases were excluded from the analysis when there were less than 2 reliable data points available on the I/O function.

TABLE 1. NUMBERS OF CHILDREN WITH CLEAR WAVEFORM COMPONENTS (ON ONE OR BOTH EARS) IN CONGENITAL AND MENINGITIC GROUPS AND STATISTICAL COMPARISONS

Waveform Component	*Congenital (n = 30)* No.	%	*Meningitic (n = 19)* No.	%	*Significance* Without Yates	With Yates
eV	28	93	12	63	p = .007	p = .02
eIII	28	93	13	68	p = .02	p = .05
eII	29	97	13	68	p = .005	p = .01

In the analysis we used the Prom-EABR data from the implanted ear only and not from both ears, because the status of the auditory pathway on 1 ear may not be independent of the other ear.

Student's *t*-test was used for analysis of variables that met the criteria for normal distributions (standardized kurtosis coefficient test < |2|, standardized skewness coefficient test < |2|, and variance ratio < the respective value corresponding to the degrees of freedom). When 1 of the distributions did not meet the above-mentioned criteria, a Mann-Whitney U test was used. A χ^2 test, with a Yates correction, was used for the statistical analysis of nonquantitative measurements. Statistical significance was accepted at the p ≤ .05 level.

RESULTS

Typical Prom-EABR waveforms are shown in the Figure, exhibiting waves eV, eIII, and eII and the short latency component. The incidences of waves eV, eIII, and eII in the congenitally and postmeningitically deaf children are illustrated in Table 1. From the 30 congenitally deaf children, 28 (93%) had a clear wave eV on at least 1 ear. This compares with 12 of 19 children (63%) in the postmeningitic group. This difference between the 2 groups was statistically significant (p = .007, and p = .02 with a Yates correction).

The latencies for the congenital group with a stimulus of 900 µA ranged from 3.9 to 6.2 ms (mean 5.0 ms) for wave eV, 2.1 to 3.2 ms (mean 2.7 ms) for

TABLE 2. COMPARISON OF WAVEFORM AMPLITUDES IN CONGENITAL AND MENINGITIC GROUPS WITH ELECTRICAL STIMULUS AT 1,000 MICROAMPERES

Waveform Component	*Congenital (n = 19)* Range	Mean	*Meningitic (n = 13)* Range	Mean	Significance
eV	0-1,990	493	0-592	176	p = .01
eIII	0-605	149	0-273	72	p = .02
eII	0-4,960	1,160	0-1,900	358	p = .02

Data are in nanovolts.

TABLE 3. COMPARISON OF WAVEFORM AMPLITUDES IN CONGENITAL AND MENINGITIC GROUPS WITH ELECTRICAL STIMULUS AT 900 MICROAMPERES

Waveform Component	Congenital (n = 27) Range	Mean	Meningitic (n = 17) Range	Mean	Significance
eV	0-1,260	369	0-428	136	p = .005
eIII	0-622	110	0-265	46	p = .009
eII	0-3,830	910	0-1,200	218	p = .02

Data are in nanovolts.

wave eIII, and 0.8 to 2.0 ms (mean 1.3 ms) for wave eII. The respective latencies for the meningitic group ranged from 4.6 to 5.7 ms (mean 5.2 ms) for wave eV, 2.2 to 3.1 ms (mean 2.7 ms) for wave eIII, and 1.2 to 1.9 ms (mean 1.5 ms) for wave eII. The only statistically significant difference in the latency of components of the Prom-EABR between the 2 groups was the mean latency of wave eV (electric stimulus 1,000 μA), which was shorter (p = .02) in the congenitally deaf children (range 3.9 to 5.8 ms, mean 4.87 ms) compared to the meningitic group (range 4.7 to 5.5 ms, mean 5.26 ms).

Tables 2-4 demonstrate the differences and the respective statistical significance of the amplitudes of waves eV, eIII, and eII between postmeningitic and congenitally deaf children. On the 9 comparisons made, all amplitudes were larger in the congenitally deaf children, and all these differences but 1 were statistically significant. In the postmeningitic group, we also compared the Prom-EABR results in implanted ears with and without obliteration (Tables 5 and 6). No statistically significant differences were found.

A comparison of the 4 parameters of the amplitude I/O function (Table 7) did not reveal any statistically significant difference between the 2 groups, except for the slope of wave eV, which was steeper (p = .04) in the congenitally deaf children.

DISCUSSION

All the significant differences in this study, regarding parameters of the Prom-EABR waveform, were in favor of better responses in the congenitally deaf children. These findings indicate a reduction in the stimulability of the cochlea of postmeningitic children that might be the result of a smaller number of surviving spiral ganglia in comparison with congenitally deaf children. However, this is not supported by findings from histologic studies in adults,[12] wherein the mean spiral ganglion cell count (12,000) in congenitally deaf adults was almost the same as the respective count in postmeningitic adults (13,000). On the other hand, the presence of a spiral ganglion cell at a light microscopic level does not guarantee normal function, and moreover, the loss of dendritic fibers may greatly exceed the loss of ganglion cell bodies.[13] Our findings suggest that the function of the peripheral spiral ganglion cells and dendrites may be impaired after meningitis.

TABLE 4. COMPARISON OF WAVEFORM AMPLITUDES IN CONGENITAL AND MENINGITIC GROUPS WITH ELECTRICAL STIMULUS AT 800 MICROAMPERES

Waveform Component	Congenital (n = 27) Range	Mean	Meningitic (n = 16) Range	Mean	Significance
eV	0-1,130	249	0-586	147	NS
eIII	0-330	91	0-241	36	p = .01
eII	0-2,960	578	0-1,200	242	p = .01

Data are in nanovolts.

NS — not statistically significant.

TABLE 5. PRESENCE OF WAVE EV IN MENINGITIC GROUP (N = 19) WITH AND WITHOUT COCHLEAR OBLITERATION

	Clear Wave eV	No Clear eV
Ears with obliteration*	7	5
Ears without obliteration	5	2

No significant difference.

*Partial or total, found in implanted ear either by computed tomography or by surgeon.

It is also reasonable to suggest that the central levels of the auditory pathways might be damaged to various extents after meningitis. This is one of the reasons that in the Nottingham Paediatric Cochlear Implant Programme, computed tomography has been replaced by magnetic resonance imaging and CISS (constructive interference in steady state) in the routine presurgical evaluation of children.[14] However, the Prom-EABR does not have the ability to reveal this type of central disorder.

It is possible that some of our results could be attributed to the partial obliteration of the cochlea in some of the postmeningitic children. However, there were 7 of 12 ears (58%) with at least partially obliterated cochleas that still demonstrated clearly identifiable wave eV components. A comparison of the

TABLE 6. PRESENCE OF WAVES EIII AND EII IN MENINGITIC GROUP (N = 19) WITH AND WITHOUT COCHLEAR OBLITERATION

	Clear eIII and eII	No Clear eIII or eII
Ears with obliteration*	8	4
Ears without obliteration	5	2

No significant difference.

*Partial or total, found in implanted ear either by computed tomography or by surgeon.

TABLE 7. COMPARISON OF FOUR PARAMETERS OF AMPLITUDE INPUT-OUTPUT FUNCTION WITH REGARD TO WAVE EV IN CONGENITAL AND MENINGITIC GROUPS

	Congenital (n = 24)		*Meningitic (n = 10)*		
	Range	*Median*	*Range*	*Median*	*p*
Slope	0-2.8 nV/μA	0.6 nV/μA	0-0.8 nV/μA	0.3 nV/μA	.04
Maximum slope	0-9.2 nV/μA	1.4 nV/μA	0.1-1.7 nV/μA	0.9 nV/μA	NS
Growth rate	0%-4.3%/μA	0.5%/μA	0.1%-1.2%/μA	0.4%/μA	NS
Maximum growth rate	0%-4.3%/μA	0.8%/μA	0.1%-1.7%/μA	0.4%/μA	NS

NS — not statistically significant.

incidence of waves eV, eIII, and eII in ears with and without any degree of cochlear obliteration (found on computed tomography or in surgery) did not reveal any significant differences, but the numbers were small.

The literature on the auditory electrophysiology of congenital and postmeningitic deafness in children is extremely limited. Gantz et al[15] found that congenitally deaf children have steeper electrically evoked whole-nerve action potential growth functions than postmeningitic children. However, they did not have sufficient numbers of children to allow a statistical comparison between the 2 groups. Mason et al,[16] using acoustic stimulation, identified a short latency component at around 3 ms, thought to be of vestibular origin, that had a significantly higher incidence in congenitally deaf children compared to a meningitic group. Damage to sensory cells in the vestibular system was suggested as the cause for loss of this component in children deafened after meningitis.

In conclusion, the results of the present study suggest that the functional status of the peripheral neurons of the auditory pathways may be more intact in congenitally deaf children than in postmeningitic children. Moreover, these electrophysiological findings provide support to recent claims that congenitally deaf children have the potential to derive as much, or even better, benefit from a cochlear implant as do prelinguistically deafened children.[3-5]

ACKNOWLEDGMENT — The authors gratefully acknowledge the clinical and scientific support of staff in the Evoked Potentials Clinic of the Medical Physics Department.

REFERENCES

1. Staller SJ, Dowell RC, Beiter AL, Brimacombe JA. Perceptual abilities of children with the Nucleus 22-channel cochlear implant system. Ear Hear 1991;12(suppl):34S-47S.

2. Uziel AS, Reuillard-Artieres F, Sillon M, et al. Speech-perception performance in prelingually deafened French children using the Nucleus multichannel cochlear implant. Am J Otol 1996;17:559-68.

3. Gantz BJ, Tyler RS, Woodworth GG, Tye-Murray N, Fryauf-Bertschy H. Results of multichannel cochlear implants in congenital and acquired prelingual deafness in children: five year follow-up. Am J Otol 1994;15(suppl 2):1-7.

4. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl 2):9-13.

5. Nikolopoulos TP, O'Donoghue GM, Robinson KL, Gibbin KP, Archbold SM, Mason SM. Multichannel cochlear implantation in post-meningitic and congenitally deaf children. Am J Otol 1997;18(suppl):s147-s148.

6. Mason SM, O'Donoghue GM, Gibbin KP, Garnham CW, Jowett CA. Peri-operative electrical auditory brainstem response in candidates for paediatric cochlear implantation. Am J Otol 1997;18:466-71.

7. Smith L, Simmons FB. Estimating eighth nerve survival by electrical stimulation. Ann Otol Rhinol Laryngol 1983;92:19-23.

8. Hall RD. Estimation of surviving spiral ganglion cells in the deaf rat using the electrically evoked auditory brainstem response. Hear Res 1990;45:123-36.

9. Fifer RC, Novak MA. Prediction of auditory nerve survival in humans using the electrical auditory brainstem response. Am J Otol 1991;12:350-6.

10. Kileny PR, Zwolan TA, Zimmerman-Phillips S, Telian SA. Electrically evoked auditory brain-stem response in pediatric patients with cochlear implants. Arch Otolaryngol Head Neck Surg 1994;120:1083-90.

11. Nikolopoulos TP, Mason SM, O'Donoghue GM, Gibbin KP. Electric auditory brainstem response in paediatric patients with cochlear implants. Am J Otol 1997;18(suppl):s120-s121.

12. Nadol JB Jr, Young Y-S, Glynn RJ. Survival of spiral ganglion cells in profound sensorineural hearing loss: implications for cochlear implantation. Ann Otol Rhinol Laryngol 1989;98:411-6.

13. Nadol JB Jr. Electron microscopic findings in presbycusic degeneration of the basal turn of the human cochlea. Otolaryngol Head Neck Surg 1979;87:818-36.

14. Nikolopoulos TP, O'Donoghue GM, Robinson KL, Holland IM, Ludman C, Gibbin KP. Preoperative radiological evaluation in cochlear implantation. Am J Otol 1997;18(suppl):s73-s74.

15. Gantz BJ, Brown CJ, Abbas PJ. Intraoperative measures of electrically evoked auditory nerve compound action potential. Am J Otol 1994;15:137-44.

16. Mason SM, Garnham CW, Hudson B. Electric response audiometry in young children prior to cochlear implantation: a short latency component. Ear Hear 1996;17:537-43.

Ann Otol Rhinol Laryngol 108:1999

MEASURING THE EFFECTS OF MENIERE'S DISEASE: RESULTS OF THE PATIENT-ORIENTED SEVERITY INDEX (MD POSI) VERSION 1

MICHAEL P. MURPHY, MD GEORGE A. GATES, MD

SEATTLE, WASHINGTON

We describe the development and initial psychometric testing of a new self-report instrument for quantifying the impact of Meniere's disease (MD) on patients' lives: the Meniere's Disease Patient-Oriented Severity Index (MD POSI). Eighty-five volunteers with chronic MD took a self-administered MD POSI. The internal consistency form of reliability was determined by calculating Cronbach's α. The relationship between total MD POSI problem severity scores and responses to a global question concerning the degree to which his or her MD had changed the patient's life assessed construct-related validity. The total problem severity score yielded excellent reliability (Cronbach's $\alpha = .928$). No significant age or gender effects were seen. A highly statistically significant association was noted between total problem severity scores and the degree to which the patient's life had been changed by his or her MD (Spearman rank correlation = .526, $p < .0001$), indicating excellent construct-related validity. The material included in the initial questionnaire provides important information that can be used clinically to quantify the impact of MD on patients' health status. A beta version of the instrument is in the process of validation and determination of its sensitivity to change in health status.

KEY WORDS — health status indicators, Meniere's disease, psychometrics, quality of life.

Meniere's disease (MD) is the most common cause of adult-onset, recurrent episodic vertigo with hearing loss.[1] People with MD are frequent visitors to physicians' offices because of the disruptive effects of their symptoms and the chronic, episodic nature of their illness. Although most patients eventually do well with existing therapy, a substantial proportion have chronic sequelae, and relatively few have prompt remission. Research into therapy should take into account the effect of the disorder upon its victims (patient-oriented data), as well as assessing the specific clinical markers of the disease. Asking about matters of importance to these people in regard to their health and well-being reveals aspects of the disease and its effect on the sufferer not detectable by the usual clinical tests. To standardize the acquisition of this patient-oriented information, we have developed and field-tested a first version of a structured history instrument designed to assess the severity of MD symptoms and MD's impact on patients' activities. We report herein the results of that field test and propose a new instrument to assess the health status of people with MD.

MATERIALS AND METHODS

Subject Selection. The subjects in this study came from 2 groups of people: the Meniere's Support Group of Sacramento and patients with MD at the University of Washington. The Sacramento support group has been active in collaborating with medical researchers, as well as providing assistance to its members. Many of the members have field-tested a monthly vertigo diary instrument for the senior author (G.A.G.). The Department of Otolaryngology–Head and Neck Surgery of the University of Washington has a long-standing interest in and experience with patients with MD.[2-6] The most recently seen 150 patients were selected for this project. With the approval of the Human Subjects Committee, a letter and questionnaire were sent to the active participants in the Sacramento group and to the University of Washington patients. This was not a random sample; rather, the patients were selected on the likelihood of their having active MD.

Questionnaire Design. The questionnaire was developed by the senior author and based on 3 decades of experience treating MD patients and on informal dialogue with colleagues. The questionnaire has 4 domains: patients' symptoms and functional status 1) during attacks and 2) between attacks, 3) the extent to which their personal feelings and activities of daily living have been affected, and 4) the employment consequences of their MD. The instrument permits one to rate the severity of symptoms and life disruptions in a standardized manner. We reasoned that the responses of the subjects would provide insight into our suppositions about what are and are not the important consequences of MD. Thus, the field test constitutes an assessment of content validity (ie, does the instrument measure what it pro-

---

From the Department of Otolaryngology–Head and Neck Surgery, University of Washington Medical Center, Seattle, Washington. This work was supported in part by grants from the Deafness Research Foundation and the National Organization for Hearing Research.

CORRESPONDENCE — George A. Gates, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Washington Medical Center, Box 357923, Seattle, WA 98195-7923.

poses to measure?) by an informed lay group with MD.

The alpha test version of the Meniere's Disease Patient-Oriented Severity Index (MD POSI) consisted of 30 items. Twenty-seven questions were posed with an ordinal response format. Twenty-three of these items inquired about both the *severity* (response scale 0 to 5) of the effect (the "problem scale") and its *importance* (response scale 1 to 4) to the respondent (the "importance scale") during the past 3 months. The 23 items were divided into 4 subscales: 4 items about effects during an attack ("during" subscale), 7 items about effects between attacks ("between" subscale), 8 items about the effect of MD on daily living activities ("daily" subscale), and 4 items about the effect of MD on the patient's occupation ("job" subscale).

Four additional ordinal response questions asked the patients to indicate 1) the degree to which their MD had changed their life overall, 2) their health compared to that of others their age, 3) their satisfaction with their MD treatment, and 4) what they expected their health to be in 5 years. Two additional questions were asked about 1) medications and 2) other therapy they had received. The final item was an unformatted comment field.

The responses were entered into a statistical analysis program (STATA v5.0). Summary statistics were prepared, and the response variation attributable to age and gender was assessed. The reliability of the 23 severity questions was estimated by determining Cronbach's α for the overall test and for subtests. The validity of the severity questions was assessed by comparing the average severity score on items 1 to 23 with the global change variable (item 24).

RESULTS

Responders. Ninety-one anonymous questionnaires were received from 53 women and 38 men. Six cases were excluded: 2 because none of the questions were answered, 1 with a different diagnosis (perilymphatic fistula), and 3 with conflicting and uninterpretable responses. The mean age of the 85 evaluable subjects was 55.7 years (range 28 to 87 years). Eighteen were from the Sacramento group and 67 were from the University of Washington group. All questions were answered by 45 (52%) people. While most subjects answered most of the questions, 13% of the severity items were omitted, with a mean number of missing severity data points of 2.6 (range of 0 to 19 overall). Of the incomplete responders, the mean number of missing items was 5.5 (SD = 4.6). Those who completed all severity questions were younger (ANOVA, F = 6.11, p = .016), but did not differ in their responses to the questions. The number of people responding to the 23 severity questions ranged from 72 to 85. The importance ranking of these questions was completed less frequently (range of number of respondents, 39 to 72). Of the 21 people who completed all items on both the severity and importance rankings, the standardized importance score (0.65) was 13 percentage points higher than the standardized severity score (0.52), a difference that was statistically significant ($t = -2.49$, $p = .022$). The remainder of this report is limited to the severity responses, as the importance rankings generally paralleled the severity rankings and did not appear to provide additional information.

Eighty-three people responded to the first health question, with 81% noting their health was good to excellent compared to that of others their age, and 19% feeling their health was poorer. All 85 rated their satisfaction with treatment (65% satisfactory to highly satisfactory, 35% unsatisfactory). Eighty-nine percent of respondents were using some form of medical therapy, usually a low-salt diet and a diuretic. Many also took other agents such as meclizine hydrochloride, a tranquilizer (Atarax or Valium), or Hismanal. Three had received streptomycin or gentamicin sulfate for labyrinthine ablation. Twelve people had undergone 1 or more surgical procedures: 10 endolymphatic sac operations, 4 vestibular nerve sections (2 had prior sac surgery), and 2 labyrinthectomies. There was no difference in gender or age between those who had an operation and those who did not have an operation. The unadjusted total severity score was lower in the nerve section and labyrinthectomy cases and higher in the endolymphatic sac surgery and aminoglycoside cases than in the nonsurgical cases. These findings should be interpreted with caution in light of the small number of subjects.

Problem Severity Scores. The average raw problem severity scores are displayed separately for the men and women in Table 1. Given the 0- to 5-point rating scale for severity, one might presume that a score of 2.5, which would indicate a midrange severity level, would be the most common score. Note that few of the responses reached this level, and most were substantially lower. There was substantial variability in the magnitude of the responses across the items, as some people indicated in their comments they were in complete remission, whereas others were having active symptoms. Some domains, such as balance, mental concentration, and (during attacks) daily activities, were substantially affected, whereas others, such as driving, recreational activities, sleep,

TABLE 1. EFFECT OF GENDER ON RAW MD POSI SCORES

Subscale Items	*MD POSI Items*	*Raw MD POSI Scores (mean ± SD)*	
		Females	*Males*
During	Hearing	2.9 ± 1.5	2.6 ± 1.6
	Balance	2.8 ± 1.7	2.8 ± 1.7
	Mental concentration (eg, reading)	2.0 ± 1.8	2.2 ± 1.6
	Performing daily activities	2.6 ± 1.8	2.6 ± 1.7
Between	Hearing	3.1 ± 1.2	3.1 ± 1.4
	Balance	2.0 ± 1.5	1.7 ± 1.4
	Mental concentration (eg, reading)	1.2 ± 1.4	1.0 ± 1.2
	Performing daily activities	1.3 ± 1.5	1.1 ± 1.4
	Sleeping	1.3 ± 1.5	0.9 ± 1.4
	Driving a car	1.0 ± 1.5	0.8 ± 1.4
	Fear of travel	1.6 ± 1.8	1.1 ± 1.4
Daily	Social life	2.6 ± 1.6	2.0 ± 1.6
	Recreational activities	2.2 ± 1.7	1.7 ± 1.5
	Being close to others	1.8 ± 1.8	1.4 ± 1.4
	Sex life	1.0 ± 1.5	1.0 ± 1.4
	Marriage	1.2 ± 1.7	1.1 ± 1.3
	Nerves	1.5 ± 1.2	1.5 ± 1.2
	General mood	2.2 ± 1.7	1.8 ± 1.2
	Outlook for the future	2.4 ± 1.7	2.1 ± 1.4
Job	Questions about my competence	1.0 ± 1.5	0.4 ± 0.8
	Questions about my reliability	1.1 ± 1.7	0.4 ± 0.8
	Job modification	1.3 ± 1.8	0.8 ± 1.4
	Loss of job/disability retirement	1.5 ± 2.1	0.7 ± 1.6
Total Problem Scale severity score*		31.9 ± 16.3	28.4 ± 17.9

MD POSI — Meniere's Disease Patient-Oriented Severity Index.

*"One"-way analysis of variance test of gender versus total problem scale severity scores indicated no statistically significant gender effects ($p = .51$).

marriage, sex life, and employment, were relatively unaffected. There were no significant gender or age differences in the responses to the severity questions.

Internal Consistency. Interitem correlations and Cronbach's coefficient of reliability (α) were calculated for the 23 severity items (1 to 23). Cronbach's α was .928 based on the raw responses to the severity questions for the 45 complete responders. (Cases with missing values cannot be included in this statistical test.) To address the impact of missing data, the items for which no response was given were adjusted by assigning a random number (0 to 5) to the missing value. The Cronbach's coefficient on the adjusted data was $\alpha = .921$, which indicates the robustness of the instrument in the face of partial completion of items. This level of reliability is quite satisfactory for an initial test of an instrument, considering that coefficients of .90 to .95 are desirable for a clinically useful instrument.[7]

Table 2 displays the crude and adjusted item-test correlation coefficients for the 23 severity items for the 85 people. The coefficient for each item compares the correlation of that item to the rest of the test; items with the largest coefficients have the greatest degree of association. This provides insight into the relative effect of that item on the full test. For example, the 2 hearing items and the sleep item had the lowest correlation with the total test score, whereas the items that asked about mood and being close to others had the highest correlations.

Table 3 displays the distribution of responses to the global items related to life change, health, health in 5 years, and satisfaction with treatment. The responses were distributed normally except for satisfaction with treatment, in which there were more cases of extreme dissatisfaction than would be expected given a trend toward a bimodal distribution. The responses to the life change, health, and health in 5 years items were significantly intercorrelated at the $p < .001$ level, with correlation coefficients of $r = .35$ to $r = .48$. Health and health in 5 years were highly correlated (Pearson's $r = .85$, $p < .0001$).

Construct Validity. The global reference question was, "Overall, my Meniere's disease has changed my life: little if any (1), to a minor degree (2), moderately (3), a lot (4), and extremely (5)." The mean score was 3.44 (median 3), and the responses were normally distributed. The response to this global

TABLE 2. CRUDE AND ADJUSTED ITEM-TEST CORRELATION COEFFICIENTS

	*Item-Test Correlation Coefficient**	
MD POSI Item	*Crude*	*Adjusted*
Hearing — during	.4351	.3843
Balance — during	.5535	.4639
Mental concentration — during	.6110	.5322
Performing daily activities — during	.6429	.5885
Hearing — between	.4387	.2302
Balance — between	.6019	.6257
Mental concentration — between	.7289	.5322
Performing daily activities — between	.7206	.7067
Sleeping — between	.4780	.4813
Driving a car — between	.6540	.6052
Fear of travel — between	.5486	.5224
Effect on social life	.7498	.7063
Effect on recreational activities	.7431	.6625
Effect on being close to others	.7511	.7328
Effect on sex life	.7082	.6416
Effect on marriage	.7132	.6585
Effect on nerves	.7323	.7006
Effect on general mood	.8462	.7924
Effect on outlook for the future	.7192	.6572
Employment — questions of competence	.5962	.5577
Employment — questions of reliability	.6984	.6225
Employment — job modification	.6869	.6612
Employment — loss of job/disability retirement	.6752	.5964
Cronbach's α	.9276	.9207

*Coefficient indicates strength of correlation of item to total test.

TABLE 3. DISTRIBUTION OF RESPONSES TO GLOBAL ITEMS RELATED TO LIFE CHANGE, HEALTH, HEALTH IN FIVE YEARS, AND SATISFACTION WITH TREATMENT

		Distribution of Responses	
Global Question	*Response*	*No.*	*%*
Overall, my Meniere's disease has changed my life	Little if any	3	3.6
	To a minor degree	12	14.3
	Moderately	29	34.5
	A lot	25	29.8
	Extremely	15	17.9
Compared to others my age, my health is	Excellent	15	18.1
	Very good	33	39.8
	Good	19	22.9
	Fair	11	13.3
	Poor	5	6.0
My satisfaction with the treatment of my Meniere's disease is	Highly satisfactory	14	16.5
	Very satisfactory	15	17.7
	Satisfactory	25	29.4
	Slightly satisfactory	13	15.3
	Very unsatisfactory	18	21.2
I expect my health in 5 years to be	Excellent	13	16.5
	Very good	29	36.7
	Good	23	29.1
	Fair	8	10.1
	Poor	6	7.6

question served as the reference parameter to compare with the specific item scores. Table 4 shows the increase in the mean composite problem severity score with increasing degree of life change due to MD. Both the raw severity scores and the adjusted severity scores (missing values filled with random numbers) are shown. The significance of this relationship was estimated by Spearman rank correlation analysis ($r = .486$ and $r = .526$ for raw and adjusted severity scores, respectively; $p < .0001$ for both). This analysis demonstrates construct validity based on the high correlation of the mean global score with the average specific item score.

DISCUSSION

Standardized history instruments are essential elements in outcomes research aimed at understanding the consequences of a disorder upon the health and well-being of affected people. There are several instruments that assess vertigo,[8,9] hearing loss,[10,11] and tinnitus,[12-17] but none are specifically directed to the MD patient. Development of such an outcomes instrument is a multistep process that begins with a concept, proceeds with a field test to assess the concept, continues with revisions based on the field test information, and undergoes external validation and, finally, assessment of the instrument's sensitivity to change.[18-23] This report describes the concept and field test stages of this research. Key issues at this stage are the reliability and validity of the instrument.

Reliability. Reliability is the degree to which an instrument is free from random error.[24] When items are used to form a scale, they should all measure the same thing and thus be correlated with one another. The standard method for assessing internal consistency is Cronbach's α, which provides an estimate of reliability based on all possible correlations between 2 sets of items within a test. For comparing groups, α values of .70 to .80 are regarded as satisfactory. For clinical applications, a minimum value of .90 is needed.[7]

The high interitem correlations and high Cronbach's α coefficient obtained in this analysis indi-

TABLE 4. MEAN RAW AND ADJUSTED MD POSI PROBLEM COMPOSITE SCORES ACCORDING TO DEGREE TO WHICH MD CHANGES PATIENTS' LIVES

		Mean MD POSI Problem Composite Scores	
Life Changed by MD	*No.*	*Raw (mean ± SD)*	*Adjusted (mean ± SD)*
Little if any	3	0.43 ± 0.72	0.43 ± 0.72
To a minor degree	8	0.96 ± 0.64	1.06 ± 0.65
Moderately	12	1.49 ± 0.74	1.62 ± 0.72
A lot	15	2.01 ± 1.07	1.96 ± 0.88
Extremely	5	3.02 ± 1.20	2.67 ± 0.96

Spearman rank correlation analysis revealed statistically significant relationship between MD POSI problem scale total scores and degree to which Meniere's disease (MD) changes patients' lives. (Spearman correlation for raw data was .48, $p < .0001$; and for adjusted data was .502, $p < .0001$.)

cate the coherence of the responses among these questions and suggest satisfactory reliability for the initial instrument, even with partial completion of the test. We believe the second version will be better in this regard. Certainly, optimal use of the instrument in a research setting will require instruction and monitoring to minimize incomplete responses.

Validity. Validity of an instrument is defined as the degree to which the instrument measures what it purports to measure.[24] There are 3 aspects of validity: criterion-related, content-related, and construct-related.

Criterion-related validity demonstrates the extent to which the scores of a new instrument are related to a "gold standard" measure. In health status assessment, criterion-related validity depends on generally accepted criterion measures. Because of the preliminary nature of this instrument, we did not attempt to assess criterion validity. The method promulgated by the American Academy of Otolaryngology–Head and Neck Surgery Committee on Hearing and Equilibrium could serve as a criterion.[25]

Accepted methods of establishing content-related validity include the use of lay and expert judgments of the appropriateness and redundancy of the items and scales of an instrument. The questionnaire items were based on professional experience and informal consultation with colleagues. The results of this analysis support the overt content, but do not address items that may have been overlooked. The extent to which these items assess the major symptoms and activity domains described by people affected by MD is affirmed by the responses. Those items most greatly affected are those most likely to have content (face) validity and to be useful in the assessment of people with MD.

Common methods of obtaining construct-related validity include an examination of the logical relationships that should exist between the instrument being evaluated and other measures and/or patterns of scores across individuals.[24] The patterns of mean MD POSI problem composite scores were examined in terms of patients' reporting increasing degrees to which their lives were affected by their MD. Our finding of a highly statistically significant relationship between the mean MD POSI problem composite score and the global change question provides preliminary support for the construct validity of the MD POSI. Construct validity will be further tested on the beta version of the MD POSI by comparing the results with those of other, well-accepted measures of MD severity.

Specific Items. The responses to specific questions were of interest. The respondents noted minimal effect on sleep, sex life, being close, marriage, employment, or driving. On the other hand, there was a substantial effect on mental concentration and daily activities both during attacks (as expected) and between attacks. The overall confidence expressed by these people in relation to their employment is notable, even though a few subjects noted job-related concerns in their comments.

Hearing loss both during and between attacks was rated as the most severe MD symptom, yet this item was poorly correlated with balance, daily activities, mental concentration, and the overall test score. This discordance may result from hearing dysfunction that is relatively fixed, in contrast to greater fluctuations in the vestibular symptoms, or it might represent an accommodation to the hearing loss. This unexpected discordance will require further investigation for clarification.

Limitations. These observations were obtained from a small, nonrandom sample of people with longstanding MD who voluntarily responded to a mailed questionnaire. These results may or may not apply to the larger group of MD sufferers or to people early in the course of their disease. To the extent these people were representative of typical MD patients, the results may be generalizable. Although the demographic characteristics and treatment history of the respondents are not atypical, it was not the purpose of this research to determine the generalizability of this sample, but rather to begin a process leading to a useful questionnaire for MD patients.

This report describes a first-generation instrument for assessing the impact of MD on people's lives. Until the second-generation instrument has been tested and validated, the ultimate usefulness of this approach remains undetermined. The responses generated by this survey have not been correlated with the clinical data and therefore should not be interpreted out of the context of this limited sample.

Completion of this questionnaire was left to the discretion of the respondent. In clinical research settings, a member of the team would instruct the respondents and oversee completion. The minimal difference in Cronbach's α between fully completed questionnaires and those completed by random numbers is encouraging in this regard.

CONCLUSION

This field test is a response to a structured inquiry from a group of people with long-standing MD. Their responses constitute a composite statement about important aspects of their lives that have been affected by MD. It would appear these people have made substantial adjustment to and compensation for their disorder and, by and large, have been able to maintain their employment and daily activities in spite of the impact of the symptoms on their lives. The greatest coherence of responses was in the domains of daily function, such as balance and mental concentration, that are adversely affected by vestibular disorders.

The instrument has been shortened by deleting the items little affected by MD (sleep, sex life, driving, hearing) and dropping the importance scale. We added a variable about ear pressure and tinnitus based on respondents' comments, and have reworded or combined other items for clarity and brevity. The revised (beta) instrument is being used in the senior author's practice. As sufficient numbers of responses accumulate, we will be able to compare the changes over time with those on other measures (audiogram, patient vertigo diary, physician evaluation). These assessments will provide an estimate of construct validity. We expect the modified instrument to be sensitive to changes in the health status of the MD patient. However, we do not yet have sufficient data to support this presumption.

ACKNOWLEDGMENTS — We thank Jack Snyder, PhD, for advice, and Janet Kelly for assistance in data management.

REFERENCES

1. Arenberg IK, Balkany TJ, Goldman G, Pillsbury RC III. The incidence and prevalence of Meniere's disease — a statistical analysis of limits. Otolaryngol Clin North Am 1980;13:597-601.

2. Snyder JM. Extensive use of a diagnostic test for Meniere's disease. Arch Otolaryngol 1974;100:360-5.

3. Snyder JM. Predictability of the glycerin test in the diagnosis of Meniere's disease. Audiology 1982;7:389-97.

4. Dobie RA, Snyder JM, Donaldson JA. Electronystagmographic and audiologic findings in patients with Meniere's disease. Acta Otolaryngol (Stockh) 1982;94:19-27.

5. Palaskas CW, Dobie RA, Snyder JM. Progression of hearing loss in bilateral Meniere's disease. Laryngoscope 1988;98:287-90.

6. Santos PM, Hall RA, Snyder JM, Hughes LF, Dobie RA. Diuretic and diet effect on Meniere's disease evaluated by the 1985 Committee on Hearing and Equilibrium guidelines. Otolaryngol Head Neck Surg 1993;109:680-9.

7. Bland MJ, Altman DG. Cronbach's alpha. BMJ 1997;314:572.

8. Hazlett RL, Tusa RJ, Waranch HR. Development of an inventory for dizziness and related factors. J Behav Med 1996;19:73-85.

9. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424-7.

10. Lamb S, Owens E, Schubert E. The revised form of the Hearing Performance Inventory. Ear Hear 1983;4:152-9.

11. Ventry I, Weinstein B. The Hearing Handicap Inventory for the Elderly: a new tool. Ear Hear 1982;3:128-34.

12. Coles RRA, Lutman ME, Axelsson A, Hazel JWP. Tinnitus severity gradings: cross-sectional studies. In: Aran JM, Dauman R, eds. Tinnitus 91: proceedings of the Fourth International Tinnitus Seminar. Amsterdam, the Netherlands: Kugler Publications, 1992:453-6.

13. Erlandsson SI, Hallberg LRM, Axelsson A. Psychological and audiological correlates of perceived tinnitus severity. Audiology 1992;31:168-79.

14. Hallam RS, Jakes SC, Hinchcliffe R. Cognitive variables in tinnitus annoyance. Br J Clin Psychol 1988;27:213-22.

15. Kuk F, Tyler RS, Russell D, Jordan H. The psychometric properties of a tinnitus handicap questionnaire. Ear Hear 1990;11:434-42.

16. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg 1996;122:143-8.

17. Wilson P, Henry J, Bowen M, Haralambous G. Tinnitus Reaction Questionnaire: psychometric properties of a measure of distress associated with tinnitus. J Speech Hear Res 1991;34:197-201.

18. Deyo RA, Centor RM. Assessing the responsiveness of functional scales to clinical change: an analogy to diagnostic test performance. J Chronic Dis 1986;39:897-906.

19. Deyo RA, Inui TS. Toward clinical applications of health status measures: sensitivity of scales to clinically important changes. Health Serv Res 1984;19:277-89.

20. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987;40:171-8.

21. Guyatt GH, Deyo RA, Charlson M, Levine MN, Mitchell A. Responsiveness and validity in health status measurement: a clarification. J Clin Epidemiol 1989;42:403-8.

22. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407-15.

23. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;47:81-7.

24. Perrin EB, Aaronson NK, Alonso J, et al. Medical Outcomes Trust Scientific Advisory Committee Instrument Review Criteria. Medical Outcomes Trust 1997;March:1-5.

25. Committee on Hearing and Equilibrium. Guidelines for the diagnosis and evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg 1995;113:181-5.

≈

ADVANCED EAR SURGERY

A Compact Training Course in Advanced Ear Surgery (Endaural Tympano-meatoplasty and Enlarged Middle Fossa Approach) will be held May 16-19, 1999, in Erlangen-Nuremberg, Germany. For information, contact Prof Dr M. E. Wigand, Dept of ORL, University of Erlangen-Nuremberg, HNO Universitatsklinik, Waldstrasse 1, D-91054, Erlangen, Germany; telephone +49/9131/85-3141; fax +49/9131/85-6857.

Ann Otol Rhinol Laryngol 108:1999

STUDY OF SYSTEMIC LUPUS ERYTHEMATOSUS IN TEMPORAL BONES

MICHIHIKO SONE, MD
NAGOYA, JAPAN
MICHAEL M. PAPARELLA, MD
MINNEAPOLIS, MINNESOTA
PATRICIA A. SCHACHERN
MINNEAPOLIS, MINNESOTA
NORIKO MORIZONO
MINNEAPOLIS, MINNESOTA

Despite some reports of sensorineural hearing loss with systemic lupus erythematosus (SLE), its pathologic correlate has remained unidentified due to the scarcity of human temporal bone studies. We here present findings in 14 temporal bones from 7 patients with SLE, examined histologically and immunohistochemically for pathologic conditions in the cochlea that might relate to their otologic histories. Blue-staining concretions were seen in the stria vascularis of 6 ears. Most of the cases showed a loss of spiral ganglion cells, with various degrees of hair cell loss and atrophy of the stria vascularis. One ear demonstrated formation of fibrous tissue and bone throughout the cochlea, with complete loss of the membranous labyrinth. Cochlear hydrops was found in only 1 ear. These findings in temporal bones from patients with SLE are discussed in relation to autoimmune disease of the inner ear.

KEY WORDS — autoimmune disease, histopathology, human temporal bone, systemic lupus erythematosus.

INTRODUCTION

Since the proposal of a new clinical entity called "autoimmune sensorineural hearing loss,"[1] there have been numerous studies of autoimmune inner ear disease (AIED), but its mechanisms have not been clearly elucidated. In some autoimmune diseases, audiovestibular manifestations are common.[2] Understanding of the pathologic correlates in AIED might be furthered by studies of temporal bones with autoimmune diseases such as polyarteritis nodosa,[2-5] relapsing polychondritis,[2,6] Cogan's syndrome,[2,7] and systemic lupus erythematosus (SLE).[5] There have been reports of disturbances in hearing in patients with SLE,[8-13] but few studies of temporal bones with SLE. The disease includes lupus nephritis ("immune complex–mediated glomerulonephritis"), and immunologic similarities have been demonstrated in the cochlea and kidney,[14,15] but unlike the kidney, the inner ear cannot be submitted to biopsy. We here examine, histologically and immunohistopathologically, cochlear disturbances in human temporal bones with SLE, to gain a better understanding of the mechanisms of AIED.

MATERIALS AND METHODS

Fourteen temporal bones from 7 patients with SLE were selected from the collection at the University of Minnesota. All had been fixed in 10% formalin, decalcified in 5% trichloroacetic acid, embedded in celloidin, and sectioned at a thickness of 20 μm. Every 10th section had been stained with hematoxylin and eosin (H & E). By methods described by Schuknecht,[16] cytocochleograms were constructed for each bone to assess the hair cells, stria vascularis, and spiral ganglion cells. Hair cells were identified as present or absent on the basis of the presence or absence of a distinct nucleus. The stria vascularis was evaluated for the estimated percentage in the loss of volume. Spiral ganglion cells were counted on the basis of the presence or absence of a distinct nucleus, and summed for each of 4 segments of the cochlea. After comparison to populations of spiral ganglion cells in age-matched normal controls described by Schuknecht,[17] the loss of spiral ganglion cells for each segment was calculated and expressed as a percentage. Slides were also assessed for vascular pathologic findings, especially focusing on vasculitis.

Immunohistochemical staining was also applied on slides of 13 of the temporal bones with SLE, 1 being unavailable for staining. In a preliminary study to test the ability to retrieve antigens from celloidin-embedded tissue, these methods had been applied to sections containing the eustachian tube. Sections were attached to slides coated with poly-L-lysine (Sigma, St Louis, Mo), and celloidin was removed with an overnight application of clove oil. Then, the slides were treated with 0.3% Triton X-100 for 10 minutes, followed by methanol and sodium hydroxide. The ABC (avidin-biotin-peroxidase complex) method was followed, using biotinylated *Bauhinia*

From the Otitis Media Research Center, Department of Otolaryngology, University of Minnesota School of Medicine, Minneapolis, Minnesota. This work was supported in part by grant P01-DC-00133 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders, by the Yokoyama Foundation, and by the International Hearing Foundation.

CORRESPONDENCE — Michihiko Sone, MD, Dept of Otorhinolaryngology, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8560, Japan.

CLINICAL FINDINGS IN SEVEN PATIENTS WITH SLE

Case	*Sex*	*Age at Death (y)*	*Duration of SLE*	*Symptoms of SLE*	*Laboratory Data*	*Otologic History*	*Primary Treatment for SLE*	*Use of Ototoxic Drugs*	*Cause of Death*
1	F	14	3 mo	Arthralgia, myalgia	FANA (+) LE test (+)	Acute otitis media	S		Sepsis
2	M	52	3 y	Renal insufficiency	Renal biopsy (+)		S, I	Furosemide	Acute myocardial infarct
3	F	22	13 y	Arthralgia, renal insufficiency	Renal biopsy (+), deposition of IC in lung	OME (bilateral PE tubes), acute SNHL on right	S, I	Furosemide	Pulmonary hemorrhage
4	F	76	5 y	Arthralgia, myalgia	FANA (+), RF (+), ALA (+)		S, I	GM	ARDS
5	F	25	12 y	Renal insufficiency	Renal biopsy (+)		S, I, hemodialysis	GM, furosemide	Sepsis
6	F	51	24 y	Renal insufficiency	Renal biopsy (+)	OME (bilateral PE tubes)	S, I, renal transplant	Furosemide	Lymphoma
7	F	47	26 y	Seizure, renal insufficiency	ACA (+), LA (+), renal biopsy (+)	Bilateral hearing loss	S, I	Furosemide	Sepsis

SLE — systemic lupus erythematosus, FANA — fluorescent antinuclear antibodies, LE — lupus erythematosus, S — steroids, I — immunosuppressive agents, IC — immune complex, OME — otitis media with effusion, PE tubes — pressure-equalizing tubes, SNHL — sensorineural hearing loss, RF — rheumatoid factor, ALA — antileukocyte antibodies, GM — gentamicin, ARDS — adult respiratory distress syndrome, ACA — anticardiolipin antibodies, LA — lupus anticoagulant.

purpurea agglutinin (BPA; Sigma) as an antibody; BPA is a lectin, and goblet cells in the eustachian tube are known to react with BPA.[18,19] Sections were developed with 3,3'-diaminobenzidine tetrahydrochloride (Dako, Carpinteria, Calif) and hydrogen peroxide. They were then counterstained with hematoxylin. Sections from the 13 temporal bones with SLE were treated with rabbit anti-human polyvalent immunoglobulins (IgG, IgA, IgM; Sigma) as primary antibodies and biotinylated goat anti-rabbit antibody (Sigma) as a secondary antibody. Some slides were pretreated with trypsin or heated water. Some slides had the CSA method applied (catalyzed signal amplification; Dako) instead of the ABC method. Negative controls consisted of omission of primary antibodies. Temporal bones from 5 patients with multiple myeloma were used as positive controls.

RESULTS

Patients' clinical findings are summarized in the Table. Ages ranged from 14 to 76, and all patients but 1 were female. The duration of the disease ranged from 3 months to 26 years. Five patients developed renal insufficiency, and others had arthralgia and myalgia. Laboratory data for diagnosis of SLE included consistent renal disease with lupus glomerulonephritis and several kinds of autoantibodies. All patients took medications, including steroids or other immunosuppressive agents. One had undergone dialysis for 7 years, and another had had a renal transplant. The cause of death in 3 of the 7 cases was sepsis.

One patient had a clinical history of acute otitis media, and 2 had had pressure-equalizing tubes inserted bilaterally in their ears. The right ear in case 3 had a history of otalgia with discharge, at the age of

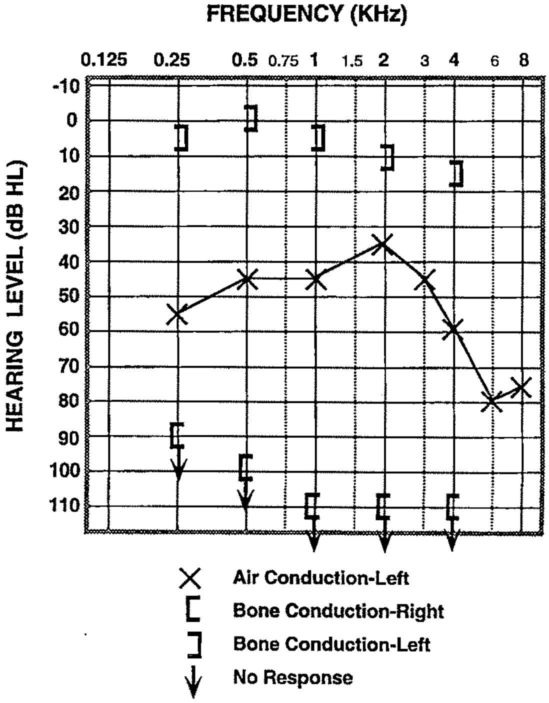


Fig 1. (Case 3) Audiogram revealing total deafness in right ear and moderate conductive hearing loss in left ear.

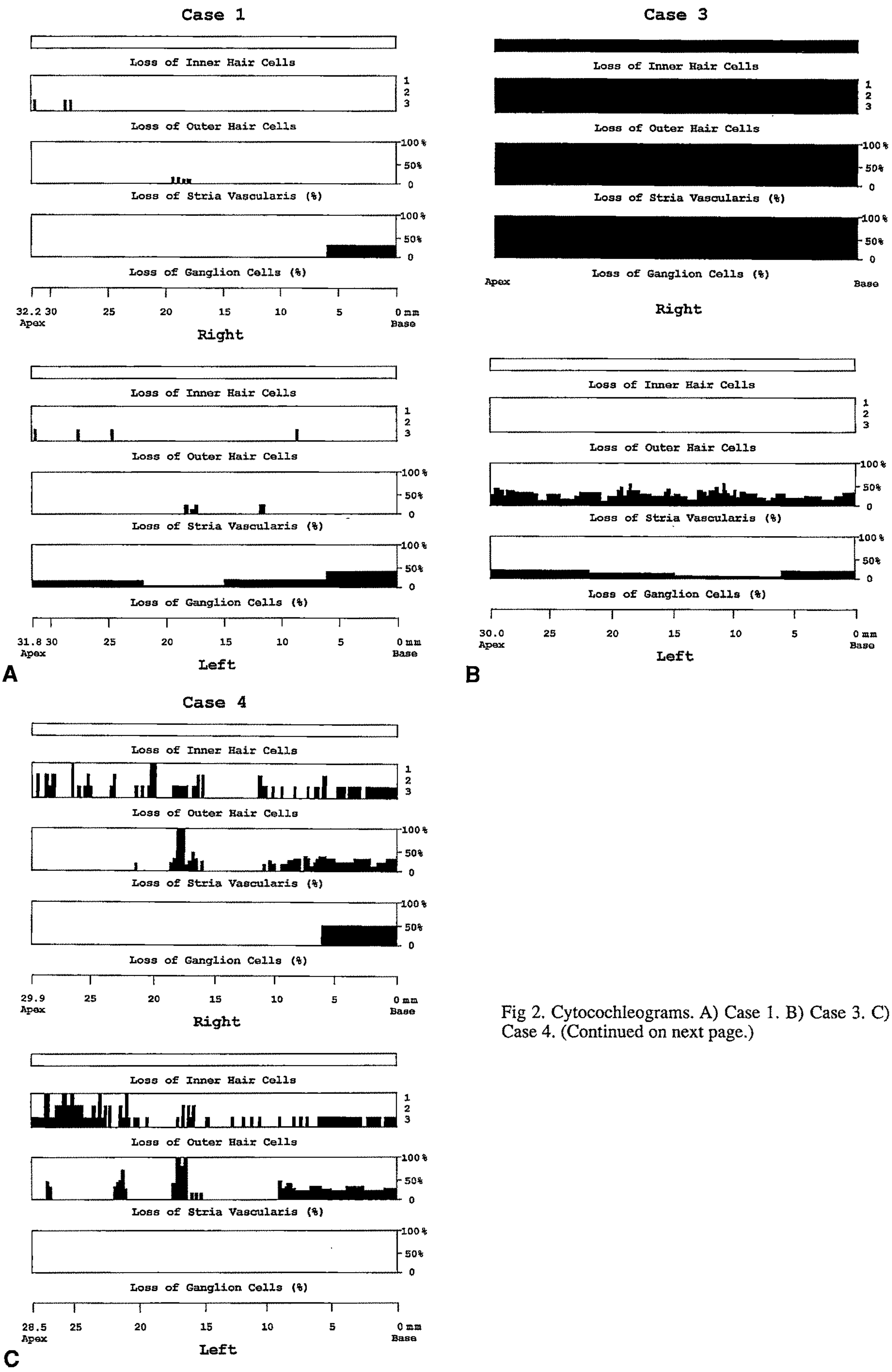


Fig 2. Cytocochleograms. A) Case 1. B) Case 3. C) Case 4. (Continued on next page.)

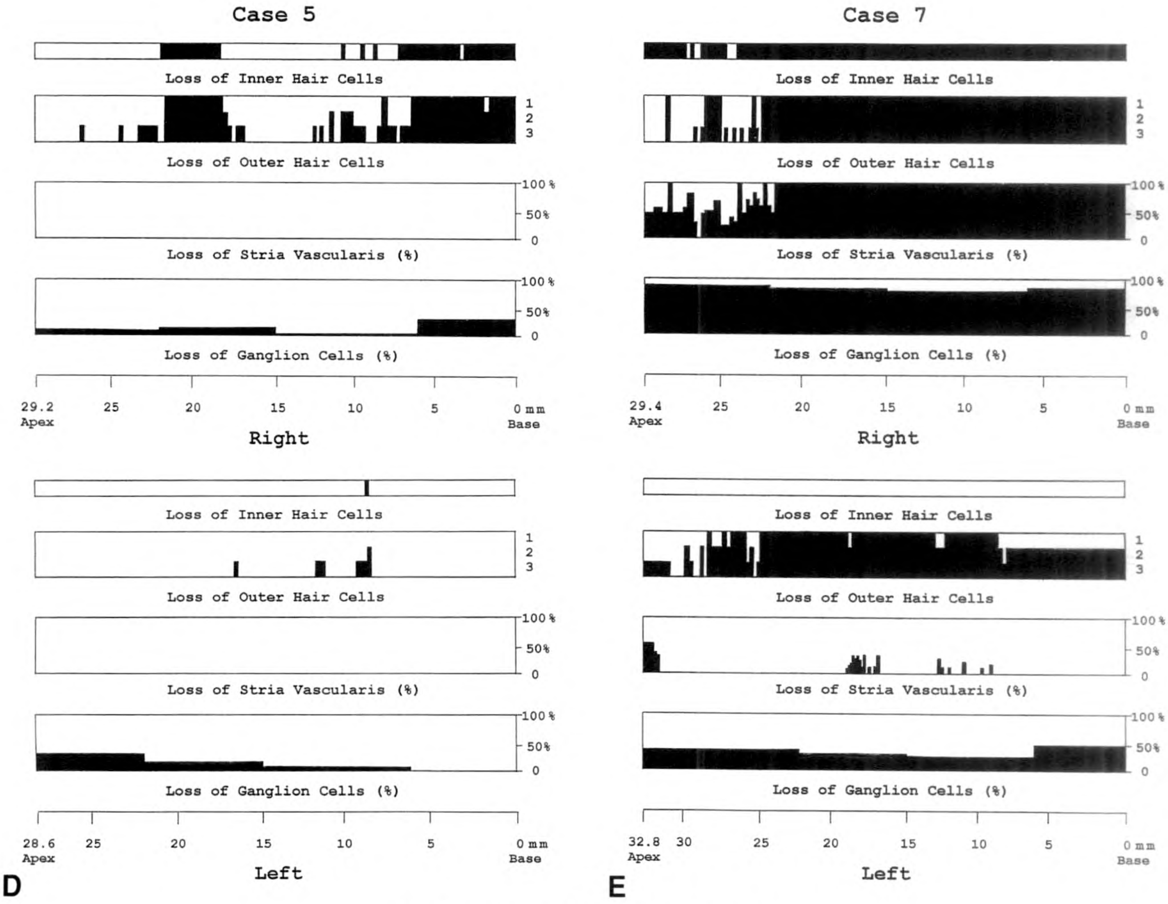


Fig 2, continued. D) Case 5. E) Case 7.

14. The patient had had normal hearing until that time. Even after 3 months of antibiotic treatment, the audiogram for that ear showed deafness (Fig 1). This case has been reported in detail previously.[5] In case 7, the patient had been deaf in the right ear from childhood, and the left ear had had about 30% of normal hearing levels according to the patient, but no audiogram was available. There were no records of special information on otologic symptoms for case 2, 4, or 5. Five patients had been treated with furosemide, and there was a history of gentamicin usage in cases 4 and 5.

Histopathologic findings in the cochlea are presented as cytocochleograms in Fig 2. In cases 2 and 6, cytocochleograms were unavailable due to postmortem artifact. Case 1 showed moderate loss of spiral ganglion cells in the first segment on the right and in all segments on the left, with scattered loss of outer hair cells and atrophy of the stria vascularis (Fig 2A). Moderate loss of hair cells and spiral ganglion cells was detected in cases 4 and 5 (Fig 2C,D). In case 5, many polymorphonuclear cells were detected in the internal auditory canal. This patient had a history of meningitis.

In case 3, the right ear showed loose fibrous tissue and new bone replacing the entire cochlea (Fig 3A), obliterating the lumen of the endolymphatic duct, displacing the round window membrane (Fig 3B), and pushing the stapedial footplate out into the middle ear. Inflammatory cells, including lymphocytes, monocytes, and polymorphonuclear cells, infiltrated the fibrous tissue. Only in this ear was vasculitis observed with vasodilation in the fibrous tissue of the cochlea. The left ear of this case also showed moderate atrophy of the stria vascularis and loss of spiral ganglion cells throughout the cochlea (Fig 2B).

Only in case 7 was cochlear hydrops observed; the right ear showed a narrowed endolymphatic duct with fibrous proliferation. There was loss of the organ of Corti in the basal and middle turns, and loss of hair cells in the apical turn. Almost all spiral ganglion cells were missing in this ear, and severe atrophy of the stria vascularis was detected (Figs 2E and 3C). The cytocochleogram showed severe loss of outer hair cells and moderate loss of spiral ganglion cells in the left ear of this patient. Another pathologic finding was blue-staining concretions in the stria vascularis (Fig 3D). Such concretions were detected in 6 temporal bones.

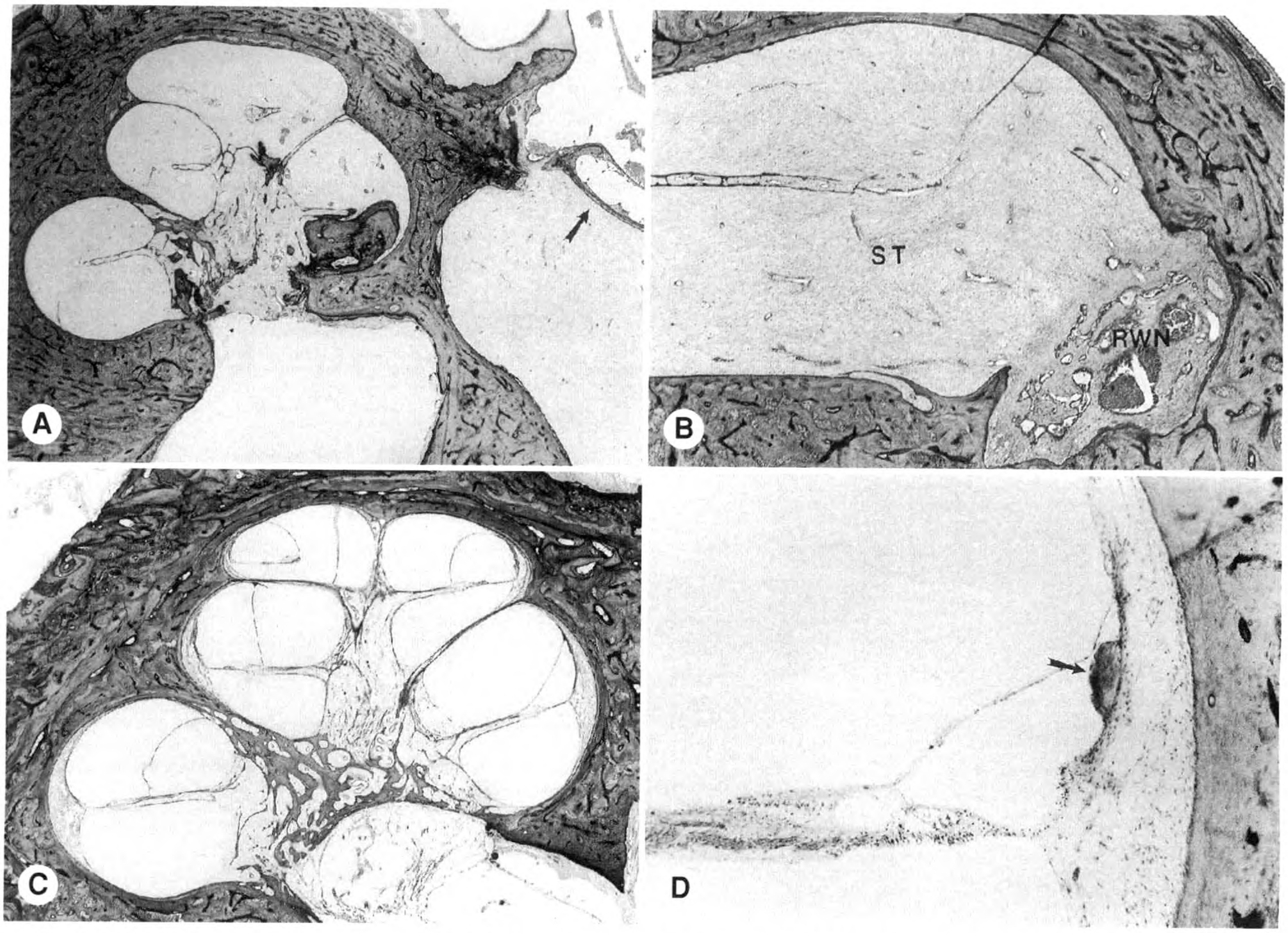


Fig 3. Histopathologic findings. A) (Case 3) Cochlea of right ear (H & E, original ×16). Organs in inner ear have been entirely replaced by loose fibrous tissue. Formation of new bone can be seen, especially in scala tympani in middle turn. In vestibule, stapedial footplate (arrow) is dislocated and pushed out into middle ear cavity by fibrous tissue. B) (Case 3) Fibrous tissue in scala tympani (ST) and granulation tissue in round window niche (RWN) in right ear (H & E, original ×30). Round window membrane has completely disappeared. C) (Case 7) Hydrops is observed throughout cochlea in right ear (H & E, original ×24). There is severe loss of spiral ganglion cells. D) (Case 4) Cochlea of right ear (H & E, original ×130). Atrophy and concretion (arrow) can be seen in stria vascularis.

Positive staining with BPA was detected in goblet cells of the eustachian tube. However, immunohistochemical staining showed no deposition of immunoglobulins in the inner ears in any of the 13 ears of the SLE patients, and none in the temporal bones of the patients with multiple myeloma.

DISCUSSION

Systemic lupus erythematosus is an autoimmune disease characterized by dysregulation of the immune system that results in production of autoantibodies, generation of circulating immune complexes (CICs), and activation of the system of immune complements.[20] There have been reports of sensorineural hearing loss (SNHL) associated with SLE, and sudden profound SNHL can be an initial symptom of SLE.[9] In a prospective study of patients with exacerbated SLE, an 8% incidence of otherwise unexplainable hearing loss was demonstrated.[8] In another prospective controlled study, 57.5% of patients with SLE were shown to have impaired hearing, especially in the low frequencies. This could suggest the possibility of a subclinical hydrops in patients with SLE,[13] but few temporal bones with SLE have been studied, and only 1 paper has been published as far as we know.[5] In our study of SLE, the cytocochleograms showed various degrees of cochlear pathologic findings. Although the pathologic findings in cases 4 and 5 could be attributed to ototoxic drug side effects, they were not typical pathologic manifestations of ototoxicity. These findings support the occurrence of an SNHL associated with SLE.

Generalized autoimmune diseases are characterized by vasculitis, considered to be caused by deposition of CICs in the walls of blood vessels. The possible target of vasculitis in the cochlea might be the stria vascularis, the spiral ligament, or the internal auditory artery.[21] Some cases of bilateral SNHL have shown responsiveness to steroids, suggesting a disease involving an immune complex (IC); some cases show improvement in hearing after administration of steroids, and deterioration of hearing and abnormal levels of CICs upon discontinuation of steroids.[22] Brookes[23] proposed possible mechanisms for the formation of ICs in the causation of SNHL, the IC being produced by antibodies due to primary infection. Alternatively, an autoantibody to tissue antigen might localize in the strial vessels, and that would lead to damage to tissues in the inner ear. In types of SNHL demonstrating elevated levels of CICs, hearing levels may be improved by plasma exchange[24]; there has been a case of SLE with recurrent bilateral SNHL being completely restored on each occasion after plasma exchange.[11] These findings indicate that SNHL associated with SLE may be a manifestation of an IC disease.

The most common systemic autoimmune diseases that involve the inner ear are polyarteritis nodosa and Cogan's syndrome.[2] The changes in the inner ear in polyarteritis nodosa have been considered to be caused by obliterative vasculitis of the labyrinthine artery,[2,3,5] which would result in ischemic necrosis; these changes therefore might not represent an autoimmune disease, in the sense that the immune system is reacting to proteins of the membranous labyrinth.[2] On the other hand, changes in the inner ear in Cogan's disease do seem to be caused by an immune response to proteins of the membranous labyrinth.[2,7] Schuknecht[2] and Schuknecht and Nadol[7] proposed that AIEDs should be characterized by the following pathologic features: 1) acute labyrinthitis resulting in atrophy of tissues in the inner ear; 2) focal and diffuse proliferation of fibrous tissue and bone; 3) frequent endolymphatic hydrops; and 4) retrograde neural degeneration. In our study of SLE, 2 patients were unilaterally deaf, and those temporal bones revealed severe loss of hair cells and spiral ganglion cells; 1 ear of 1 patient demonstrated loose fibrosis and formation of new bone in the cochlea. Another patient demonstrated cochlear hydrops in 1 ear.

Neurologic abnormalities have been demonstrated in patients with SLE.[25] Several kinds of pathogenesis appear to be involved in lupus of the nervous system, including autoantibody-mediated disease and vasculitis.[26] The findings of spiral ganglion cell loss with no or only scattered loss of outer hair cells, in bilateral ears of case 1 and the left ear of case 3, may support the theory that the cochlear nerve is primarily involved in the hearing disturbances caused by SLE. Blue-staining concretions in the stria vascularis, detected in 6 ears in this study, have been reported to be observed frequently in temporal bones of patients who had suffered chronic renal failure that had been treated with hemodialysis and kidney transplantation,[27] but these concretions in the stria vascularis in our study have remained unidentified with such etiologic associations.

The glomerulonephritis associated with SLE is considered to be a typical IC-mediated disease. Immunologically, there are antigenic similarities between the stria vascularis and the glomerular basement membrane.[14,15] A study using a substrain of New Zealand Black mice (which spontaneously develop a disease closely resembling human SLE) demonstrated that deposits of anti-mouse IgM antibody in the stria vascularis of these mice could cause strial damage that resulted in hearing dysfunction.[28] We treated slides with methanol–sodium hydroxide,[29] trypsin, or heated water and application of the CSA method.[30] In our present study, this immunohistochemical staining did not reveal deposition of immunoglobulins in the inner ear. The positive staining with BPA detected in goblet cells provided evidence that the technique of antigen retrieval from celloidin-embedded tissue was effective. Immunoglobulins are glycoproteins, similar to BPA. We believe there are 3 possible reasons for the absence of immunoglobulin deposition.

First, on the basis of our negative findings in the temporal bones with multiple myeloma, we believe that the absence of antibody staining is due to the antigenic instability of immunoglobulin (including ICs) under long exposure to formalin and acid (in the previously embedded slides). Further, the number of temporal bones examined in our study was quite small, and case 3 was the only one presenting rapidly progressive hearing loss that might coincide with clinical features of AIED. Moreover, therapy for SLE that used steroids and immunosuppressives might have been responsible for the absence of demonstrably pathologic vascular findings at autopsy.[3]

It is well known that patients with SLE have a predilection for developing infection,[25] and in 3 of our 7 patients the cause of death was sepsis. Considering such a predilection in relation to the inner ear, we found that in the right ear of our case 3, the round window membrane had been completely displaced by fibrous tissue, and there was granulation tissue in the round window niche. This might indicate that pathologic findings in the cochlea were induced by disease from the middle ear invading through the round window membrane. There was, however, severe vasculitis detected in that inner ear, and vasculitis in SLE is most commonly due to local deposition of ICs in the walls of blood vessels. In case 3, deposition of ICs had been detected in the alveolar walls of the lung, suggesting the presence of CICs in this case. On the other hand, the cellular pathologic findings of vascular disease in SLE can be classified into 2 categories — inflammation and thrombosis — and such a cellular mechanism might underlie the findings in this ear.[20] In case 3, fibrous tissue and formation of new bone were also detected in all semicircular canals; this finding coincides with the pathologic features that Schuknecht[2] and Schuknecht and Nadol[7] proposed as characterizing AIED. These pathologic changes are consistent with an inflammatory attack on the membranous labyrinth.[7] On the basis of these pathologic findings and the clinical history of progressive hearing loss, case 3 might therefore be considered to represent autoimmune changes in the inner ear.

The pathogenesis of AIED could be multifactorial. Underlying generalized autoimmune diseases would themselves influence pathologic conditions in the inner ear, as would autoimmune responses in the inner ear itself. Nevertheless, we need further studies of temporal bones with autoimmune diseases to give us clues to understanding the mechanisms of AIED.

ACKNOWLEDGMENTS — We thank Sherry Fulton for the photography, and Ginny Hansen for editing the manuscript.

REFERENCES

1. McCabe BF. Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 1979;88:585-9.
2. Schuknecht HF. Ear pathology in autoimmune disease. Adv Otorhinolaryngol 1991;46:50-70.
3. Gussen R. Polyarteritis nodosa and deafness: a human temporal bone study. Arch Otorhinolaryngol 1977;217:263-71.
4. Yanagita N, Yokoi H, Koide J, Toriyama M, Ishii T. Acute bilateral deafness with nephritis: a human temporal bone study. Laryngoscope 1987;97:345-52.
5. Yoon TH, Paparella MM, Schachern PA. Systemic vasculitis: a temporal bone histopathologic study. Laryngoscope 1989;99:600-9.
6. Hoshino T, Ishii T, Kodama A, Kato I. Temporal bone findings in a case of sudden deafness and relapsing polychondritis. Acta Otolaryngol (Stockh) 1980;90:257-61.
7. Schuknecht HF, Nadol JB. Temporal bone pathology in a case of Cogan's syndrome. Laryngoscope 1994;104:1135-42.
8. Bowman CA, Linthicum FH, Nelson RA, Mikami K, Quismorio F. Sensorineural hearing loss associated with systemic lupus erythematosus. Otolaryngol Head Neck Surg 1986; 94:197-204.
9. Caldarelli DD, Rejowski JE, Corey JP. Sensorineural hearing loss in lupus erythematosus. Am J Otol 1986;7:210-3.
10. Narula AA, Powell RJ, Davis A. Frequency-resolving ability in systemic lupus erythematosus. Br J Audiol 1989;23: 69-72.
11. Hamblin TJ, Mufti GJ, Bracewell A. Severe deafness in systemic lupus erythematosus: its immediate relief by plasma exchange. Br Med J [Clin Res] 1982;284:1374.
12. Fradis M, Podoshin L, Ben-David J, Statter P, Pratt H, Nahir M. Brainstem auditory evoked potentials with increased stimulus rate in patients suffering from systemic lupus erythematosus. Laryngoscope 1989;99:325-9.
13. Andonopoulos AP, Naxakis S, Goumas P, Lygatsikas C. Sensorineural hearing disorders in systemic lupus erythematosus: a controlled study. Clin Exp Rheumatol 1995;13:137-41.
14. Quick CA, Fish A, Brown C. The relationship between cochlea and kidney. Laryngoscope 1973;83:1469-82.
15. Arnold W. Inner ear and renal diseases. Ann Otol Rhinol Laryngol Suppl 1984;93(suppl 112):119-24.
16. Schuknecht HF. Pathology of the ear. 2nd ed. Philadelphia, Pa: Lea & Febiger, 1993.
17. Schuknecht HF. Auditory and cytocochlear correlates of inner ear disorders. Otolaryngol Head Neck Surg 1994;110:530-8.
18. Ueno K, Lim DJ. Heterogeneity of glycoconjugates in the secretory cells of the chinchilla middle ear and eustachian tubal epithelia: a lectin-gold cytochemical study. J Histochem Cytochem 1991;39:71-80.
19. Haruna S, Schachern PA, Paparella MM, Sano S, Haruna Y, Haruta A. Glycoconjugates in cats and chinchillas following eustachian tube obstruction. In: Lim DJ, Bluestone CD, Casselbrant M, Klein JO, Ogra PL, eds. Recent advances in otitis media. Hamilton, Canada: BC Decker, 1996:545-8.
20. Belmont HM, Abramson SB, Lie JT. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Arthritis Rheum 1996;39:9-22.
21. Veldman JE, Roord JJ, O'Connor AF, Shea JJ. Autoimmunity and inner ear disorders: an immune-complex mediated sensorineural hearing loss. Laryngoscope 1984;94:501-7.
22. Kanzaki J, Ouchi T. Steroid-responsive bilateral sensorineural hearing loss and immune complexes. Arch Otorhinolaryngol 1981;230:5-9.
23. Brookes GB. Immune complex-associated deafness: preliminary communication. J R Soc Med 1985;78:47-55.
24. Brookes GB, Newland AC. Plasma exchange in the treatment of immune complex–associated sensorineural deafness. J Laryngol Otol 1986;100:25-33.
25. Petri M. Clinical features of systemic lupus erythematosus. Curr Opin Rheumatol 1995;7:395-401.
26. Denburg JA, Denburg SD, Carbotte RM, Sakic B, Szechtman H. Nervous system lupus: pathogenesis and rationale for therapy. Scand J Rheumatol 1995;12:263-73.
27. Oda M, Preciado MC, Quick CA, Paparella MM. Labyrinthine pathology of chronic renal failure patients treated with hemodialysis and kidney transplantation. Laryngoscope 1974; 84:1489-506.
28. Sone M, Nariuchi H, Saito K, Yanagita N. A substrain of NZB mouse as an animal model of autoimmune inner ear disease. Hear Res 1995;83:26-36.
29. Shi SR, Coté C, Kalra KL, Taylor CR, Tandon AK. A technique for retrieving antigens in formalin-fixed, routinely acid-decalcified, celloidin-embedded human temporal bone sections for immunohistochemistry. J Histochem Cytochem 1992; 40:787-92.
30. Bobrow MN, Harris TD, Shaughnessy KJ, Litt GJ. Catalyzed reporter deposition, a novel method of signal amplification: application to immunoassays. J Immunol Methods 1989; 125:279-85.

Ann Otol Rhinol Laryngol 108:1999

EFFECTS OF EPINEPHRINE ON OUABAIN-SENSITIVE, K^+-DEPENDENT *P*-NITROPHENYLPHOSPHATASE ACTIVITY IN STRIAL MARGINAL CELLS OF GUINEA PIGS

NAOYUKI KANOH, MD, PHD
NISHINOMIYA, JAPAN

In strial marginal cells, Na^+/K^+-ATPase activity is abundant, and contributes to maintain the characteristic electrolyte composition of the cochlear endolymph. In the present study, to clarify the relationship between epinephrine and strial Na^+/K^+-ATPase activity, the ouabain-sensitive, K^+-dependent *p*-nitrophenylphosphatase (K^+-NPPase) activity of strial marginal cells was investigated with a cerium-based method in normal guinea pigs and guinea pigs treated with reserpine, epinephrine, and reserpine plus epinephrine. In our previous study, K^+-NPPase activity had almost completely decreased 3 to 20 days after reserpine administration. In the present study, at 10 days after reserpinization and following repeated epinephrine treatment, enzyme activity was detectable. These results suggest that exogenous epinephrine was able to restore strial K^+-NPPase activity in the reserpine-treated animals, and that epinephrine might increase strial Na^+/K^+-ATPase activity.

KEY WORDS — epinephrine, humoral control, K^+-NPPase cytochemistry, reserpine, stria vascularis.

INTRODUCTION

Sodium/potassium-activated adenosine triphosphatase (Na^+/K^+-ATPase) is a ubiquitous plasma membrane enzyme that catalyzes the movement of K^+ into cells in exchange for Na^+. In addition, it provides the driving force for the transport of other solutes, notably, amino acids, sugar, and phosphate.[1] In strial marginal cells, Na^+/K^+-ATPase activity is high on the basolateral infoldings, and contributes to the characteristic electrolyte composition of the cochlear endolymph.[2-5] However, the stria vascularis has been reported not to be innervated.[6-8]

In the rat brain[9] and in subcellular fractions of rat brain,[10] epinephrine was reported to activate Na^+/K^+-ATPase activity. Through increased cAMP and activation of the protein kinase A pathway, epinephrine also stimulated the skeletal muscle Na^+/K^+-ATPase.[11]

Reserpine is an adrenergic neuron blocker, and high doses of reserpine induce depletion of biogenic amines. In strial marginal cells, Kanoh et al[12,13] reported that reserpine decreased ouabain-sensitive, K^+-dependent *p*-nitrophenylphosphatase (K^+-NPPase) activity from day 3 to day 20 after treatment. Kanoh et al[14,15] also reported that dopamine decreased strial K^+-NPPase activity. K^+-NPPase was reported to be the second component of the Na^+/K^+-ATPase complex, which represents the dephosphorylation step in the sodium pump cycle.[16] However, no studies on strial Na^+/K^+-ATPase activity have been reported in relation to the regulation of the stria vascularis by epinephrine.

In the present study, to clarify the effect of epinephrine on K^+-NPPase activity of strial marginal cells, the K^+-NPPase activity was cytochemically estimated in untreated normal animals and after reserpine, epinephrine, and reserpine plus epinephrine administrations.

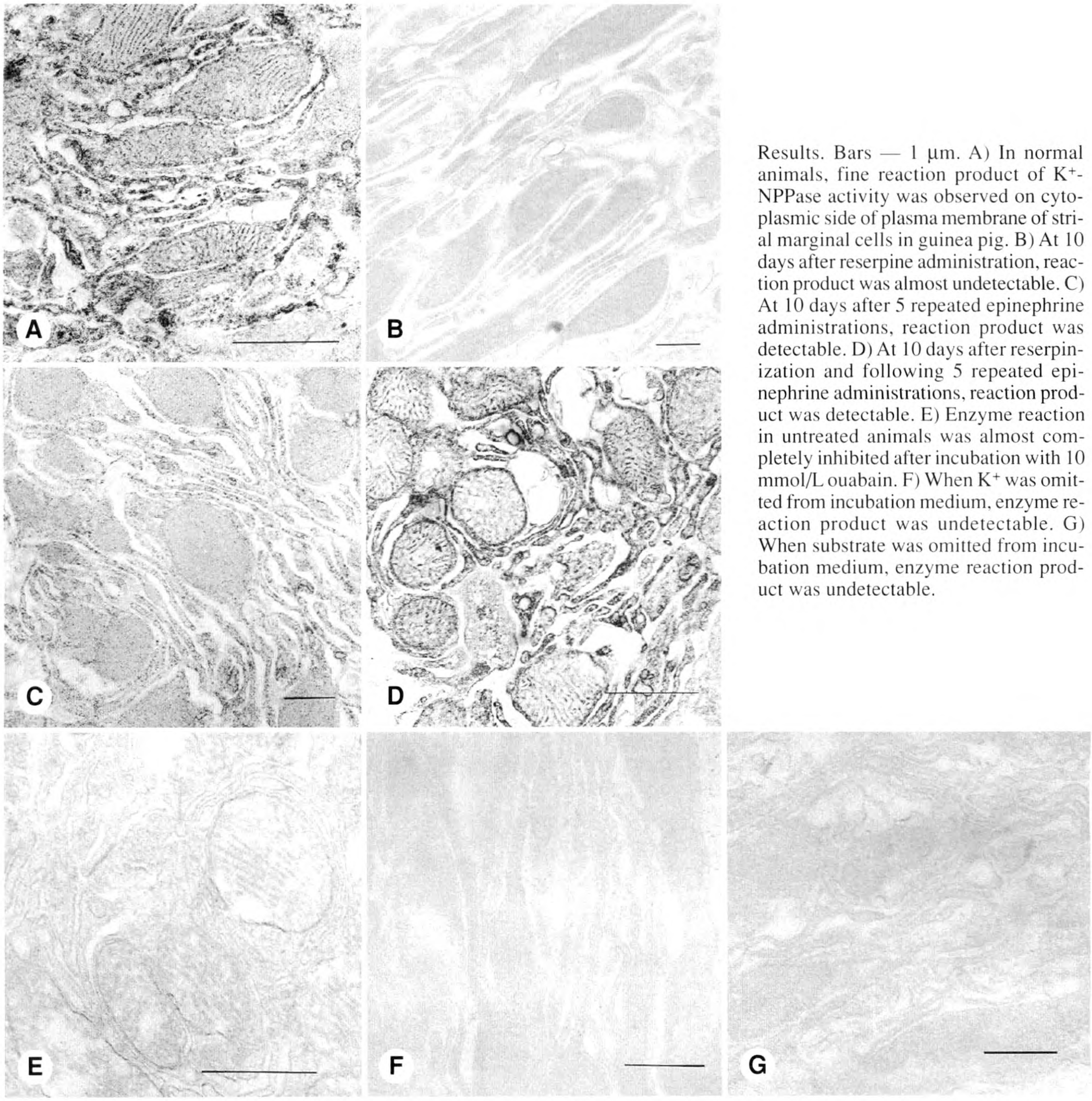
MATERIALS AND METHODS

Animals. Striae vasculares of the cochlear ducts were obtained from 11 Hartley guinea pigs, weighing 400 to 500 g, with a normal Preyer's reflex. The experimental animals were divided into the following 3 groups. The first group consisted of 4 normal untreated animals. The second group was painlessly sacrificed at 10 days after 5 repeated epinephrine administrations (0.1 mg/kg 5 times; the first, third, fifth, seventh, and ninth days; intramuscular injection; n = 3 guinea pigs). The third group was painlessly sacrificed at 10 days after reserpine administration (10 mg/kg, intraperitoneal injection) and following 5 repeated epinephrine administrations (0.1 mg/kg 5 times; the first, third, fifth, seventh, and ninth days; intramuscular injection; n = 4). In the experi-

---

From the Department of Otolaryngology, Hyogo College of Medicine, Nishinomiya, Japan. This paper was supported by a Grant in Aid for Science Research from the Ministry of Education, Science and Culture of Japan (08671998). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Hyogo College of Medicine.

CORRESPONDENCE — Naoyuki Kanoh, MD, PhD, Dept of Otolaryngology, Hyogo College of Medicine, 1-1, Mukogawacho, Nishinomiya, Hyogo 663-8501, Japan.



Results. Bars — 1 µm. A) In normal animals, fine reaction product of K^+-NPPase activity was observed on cytoplasmic side of plasma membrane of strial marginal cells in guinea pig. B) At 10 days after reserpine administration, reaction product was almost undetectable. C) At 10 days after 5 repeated epinephrine administrations, reaction product was detectable. D) At 10 days after reserpinization and following 5 repeated epinephrine administrations, reaction product was detectable. E) Enzyme reaction in untreated animals was almost completely inhibited after incubation with 10 mmol/L ouabain. F) When K^+ was omitted from incubation medium, enzyme reaction product was undetectable. G) When substrate was omitted from incubation medium, enzyme reaction product was undetectable.

ments involving reserpinization, striae vasculares obtained from untreated guinea pigs were studied simultaneously for positive enzyme reactivity.

Preparation of Tissue. Under deep anesthesia with ketamine hydrochloride (intramuscular injection), the animals were perfused through the heart with a fixative containing 2% paraformaldehyde and 0.05% glutaraldehyde in 0.1 mol/L cacodylate buffer, pH 7.4. After decapitation, the temporal bones were excised under a stereomicroscope, and the striae vasculares were carefully dissected from the cochlear ducts and immersed in the same fixative for 1 hour at 4°C.

Cytochemical Procedure. Striae vasculares were rinsed with 50 mmol/L Tricine buffer, pH 7.5, for 15 minutes, and incubated in the medium used by Kobayashi et al.[17] The incubation medium contained 50 mmol/L Tricine buffer, pH 7.5, 2 mmol/L cerium chloride as the capture agent, 10 mmol/L magnesium chloride, 50 mmol/L potassium chloride, and 2 mmol/L *p*-NPP (magnesium salt) as the substrate, and 5% sucrose, 2.5 mmol/L levamisole (an inhibitor of alkaline phosphatase), and 0.00015% Triton X-100 to facilitate penetration of the incubation medium. The medium was filtered through 0.22-µm pore size filters after the pH was adjusted to 7.5. The incubation was performed for 45 minutes at 37°C in a shaking incubator. Tissue samples were washed for 10 minutes with 0.1 mmol/L Tris-maleate buffer at pH 6.0, then processed for electron microscopy. In control experiments to determine negative enzyme reactivity, tissue samples were incubated in a substrate-free medium, in a medium containing 10 mmol/L ouabain, and in a medium in which K$^+$ had been replaced with Na$^+$.

Electron Microscopy. After cytochemical incubation, the tissues were post-fixed with 2% osmium tetroxide in 0.2 mol/L cacodylate buffer, pH 7.4, for 1 hour at room temperature. The specimens were then dehydrated through a graded series of alcohol solutions and propylene oxide and then embedded in Spurr's epoxy resin. Thin sections were cut on an Ultracut OmU4 ultramicrotome (C. Reichert AG, Vienna, Austria) and picked up with copper grids. Uncontrasted ultrathin sections were then observed under a JEM-1200 electron microscope (Jeol Co, Tokyo, Japan).

RESULTS AND DISCUSSION

The present cytochemical examination of K$^+$-NPPase activity in normal untreated animals revealed fine granular reaction products on the cytoplasmic side of the infolded plasma membrane of strial marginal cells (see Figure, A). At 10 days after reserpine administration, reaction product was almost undetectable (see Figure, B). At 10 days after 5 repeated epinephrine administrations (see Figure, C), reaction product was detectable on the basolateral infoldings of strial marginal cells in 4 animals. At 10 days after reserpinization and following 5 repeated epinephrine administrations (see Figure, D), reaction product was detectable on the basolateral infoldings of strial marginal cells in 4 of the 5 investigated animals. In the negative control experiments, the enzyme reaction in untreated animals was almost completely inhibited by incubation with 10 mmol/L ouabain (see Figure, E). When K$^+$ was replaced with Na$^+$ (see Figure, F), and when the substrate was omitted from the incubation (see Figure, G), the enzyme reaction product was almost undetectable.

Reserpine releases biogenic amines such as norepinephrine, epinephrine, dopamine, and serotonin from storage or binding sites in the central and peripheral nervous systems. Thus, high doses of reserpine induce the depletion of these amines. The dose of reserpine used in the present study (10 mg/kg) was thought to be high enough to completely abolish catecholamine activity. In previous studies, transporting Na$^+$/K$^+$-ATPase activity on the internodal axolemma of the guinea pig facial nerve was found to be decreased after reserpine administration,[18] and the potassium concentration of the cochlear endolymph was found to be decreased at 24 hours after reserpine administration.[4] These results indicated that catecholamines might be essential to maintaining normal Na$^+$/K$^+$-ATPase activity.

In the present study, strial K$^+$-NPPase activity after 5 repeated epinephrine administrations alone was found to be positive. After reserpinization and following epinephrine administration, strial K$^+$-NPPase activity was found to be positive, and epinephrine was able to restore K$^+$-NPPase activity. These experiments indicate that epinephrine produces increased strial Na$^+$/K$^+$-ATPase activity, which is similar to the reaction of Na$^+$/K$^+$-ATPase in the brain[9,10] and muscle.[11]

Thus, the function of the stria vascularis in producing cochlear endolymph may be regulated by one of the representative catecholamines, epinephrine.

REFERENCES

1. Ewart HS, Klip A. Hormonal regulation of the Na$^+$-K$^+$-ATPase: mechanisms underlying rapid and sustained changes in pump activity. Am J Physiol 1995;269:C295-C311.
2. Smith CA, Lowry OH, Wu ML. Electrolytes of labyrinthine fluids. Laryngoscope 1954;64:141-53.
3. Sterkers O, Ferrary E, Amiel C. Production of inner ear fluids. Physiol Rev 1988;68:1083-128.
4. Kanoh N, Makimoto K. Effects of reserpinization on the electrolytes distribution in inner ear fluids of guinea pig. Acta Otolaryngol (Stockh) 1984;98:98-104.
5. Kanoh N, Makimoto K. The effects of peroral glycerol administration on inner ear fluid electrolytes of guinea pigs. Ann Otol Rhinol Laryngol 1985;94:319-21.
6. Terayama Y, Holz E, Beck C. Adrenergic innervation of the cochlea. Ann Otol Rhinol Laryngol 1966;75:69-86.
7. Spoendlin H, Lichtensteiger W. The adrenergic innervation of the labyrinth. Acta Otolaryngol (Stockh) 1966;61:423-34.
8. Shibamori Y, Tamamaki N, Saito H, Nojyo Y. The trajectory of the sympathetic nerve fibers to the rat cochlea as revealed by anterograde and retrograde WGGA-HRP tracing. Brain Res 1994;646:223-9.
9. Wu PH, Phillis JW. Characterization of receptor-mediated catecholamine activation of rat brain cortical Na$^+$-K$^+$-ATPase. Int J Biochem 1980;12:353-9.
10. Schaefer A, Unyi G, Pfeifer AK. The effects of a soluble factor and of catecholamines on the activity of adenosine triphosphatase in subcellular fractions of rat brain. Biochem Pharmacol 1974;23:2257-71.
11. Clausen T, Hansen O. Active Na-K transport and the rate of ouabain binding. The effect of insulin and other stimuli on skeletal muscle and adipocytes. J Physiol (Lond) 1977;270:415-30.
12. Kanoh N, Kumoi T, Okada T, Seguchi H. Ultracytochemical study of ouabain-sensitive, K$^+$-dependent *p*-nitrophenylphosphatase activity in the stria vascularis of reserpinized guinea pigs. Acta Otolaryngol (Stockh) 1993;113:142-5.
13. Kanoh N. Reserpine inhibits the Na-K ATPase activity

of the stria vascularis in the cochlea. Laryngoscope 1994;104: 197-200.

14. Kanoh N. Dopamine inhibits the Na-K ATPase activity of the stria vascularis in the cochlea. Acta Otolaryngol (Stockh) 1995;115:27-30.

15. Kanoh N, Ogasawara H, Mohri D, Fukazawa K, Sakagami M. Cytochemical effects of in vitro dopamine treatment on the Na-K ATPase activity in strial marginal cells. Acta Otolaryngol (Stockh) 1996;116:824-7.

16. Judah JD, Ahmed K, McLean AEM. Ion transport and phosphoproteins of human red cells. Biochim Biophys Acta 1962;65:472-84.

17. Kobayashi T, Okada T, Seguchi H. Cerium-based cytochemical method for detection of ouabain-sensitive, potassium-dependent, *p*-nitrophenylphosphatase activity at physiological pH. J Histochem Cytochem 1987;35:601-11.

18. Kanoh N. Cytochemical localization of ouabain-sensitive, K+-dependent, *p*-nitrophenylphosphatase activity in the facial nerve of reserpinized guinea pigs. J Histochem Cytochem 1997;45:1129-35.

≈

INTERNATIONAL MEETING ON OTOLOGY

The International Meeting on Otology of the Jean Causse Ear Clinic will be held June 5, 1999, in Béziers, France. For more information, please contact Robert Vincent, MD, Jean Causse Ear Clinic, Traverse de Béziers, 34440 Colombiers, France; telephone (33) 4-67-35-62-62; fax (33) 4-67-35-62-00.

Ann Otol Rhinol Laryngol 108:1999

GUIDED TISSUE GENERATION IN THE TEMPORAL BONE

GÖSTA GRANSTRÖM, MD, DDS, PHD
ANDERS TJELLSTRÖM, MD, PHD
GOTHENBURG, SWEDEN

Ten patients with malformations of the temporal bones were submitted to installation of implants for anchorage of bone-anchored auricular epistheses or bone-anchored hearing aids. Due to lack of bone in the temporal region, expanded polytetrafluoroethylene membranes were used to aid bone generation, each patient serving as his or her own control. It was found that bone formation around the flange fixtures covered with membranes increased significantly compared to the uncovered fixtures. It is concluded that the use of barrier membranes is one way to support bone generation in temporal bones lacking sufficient bone for implant-related surgery.

KEY WORDS — bone promotion, expanded polytetrafluoroethylene barrier membranes, titanium implants.

INTRODUCTION

The osseointegration concept is nowadays an established practice for the rehabilitation of patients with defects of the craniofacial region. It is especially useful for patients with ear, orbit, or nose defects. During the 20 years that now have elapsed since the first patient received an extraoral osseointegrated implant in the temporal bone, more than 8,000 extraoral fixtures of the Brånemark system type have been inserted in more than 4,000 patients (Nobel Biocare, Gothenburg, Sweden, sales statistics, 1996). It was originally only used in adult patients, but with time, and as our confidence with the concept grew, it has further been used in the younger population. The indication to use the concept in children 2 to 15 years of age has especially been due to malformations of the ear. There are 2 reasons to rehabilitate children with ear malformations. The first is the functional aspect; by using a bone-anchored hearing aid (BAHA), the child can obtain social hearing and thence develop language.[1] The second aspect is esthetic. Bone-anchored ear epistheses (BAEs) help the patient become better integrated into society.[2]

Over the years, we have experienced some problems related to osseointegration surgery in the temporal bone of children. The bone is generally softer, with marrow spaces scattered in the mastoid area. The cortex is very thin, and sometimes dura recesses give the surgeon less than 2 mm of bone to insert fixtures into (Fig 1). The malformed temporal bone might also show anatomic defects that actually make insertion of fixtures for osseointegration impossible because the bone is too thin. Alternatives to obtaining enough bone might be bone grafting, inserting shorter fixtures, or the use of guided tissue regeneration.[3] The purpose of the present investigation was

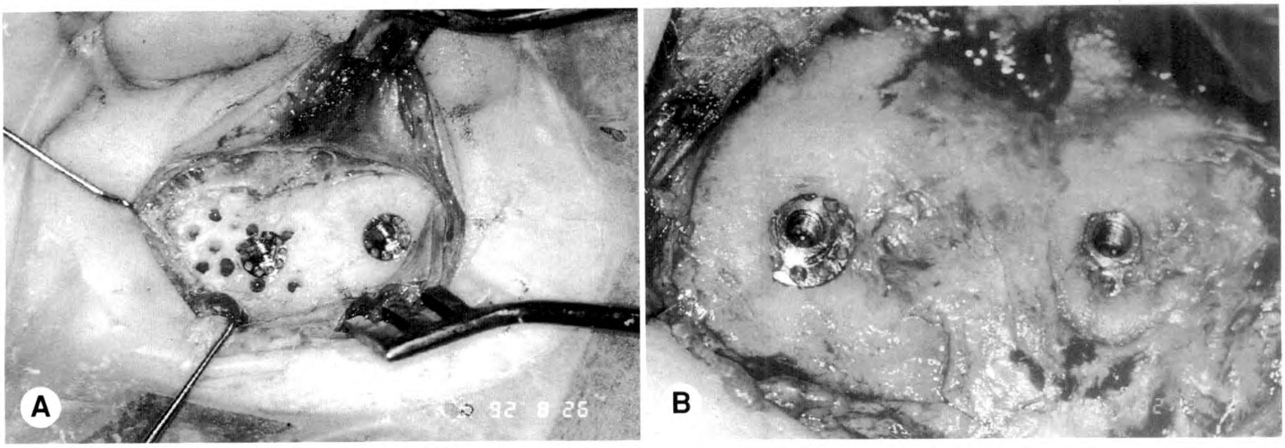


Fig 1. Surgery in temporal bone for bone-anchored auricular prosthesis. A) First stage. Upper fixture is well inserted in temporal line, whereas lower implant could be inserted only after 11th hole was drilled. B) Same patient at second-stage surgery, 4 months later. As can be seen, both fixtures are clinically well integrated in bone, bone is growing over flanges, and there are no remnants of earlier drilled holes in mastoid area.

From the Department of Otolaryngology–Head and Neck Surgery, University of Gothenburg, Gothenburg, Sweden. This study was supported by grants from the Swedish Medical Research Council, project B93-17X-10397-01A, the Magnus Bergvall Foundation, the First of May Flower Annual Campaign, The Sven Jerring Foundation, the Samariten Foundation, and the Åhlén Foundation.

CORRESPONDENCE — Gösta Granström, MD, DDS, PhD, ENT Division, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden.

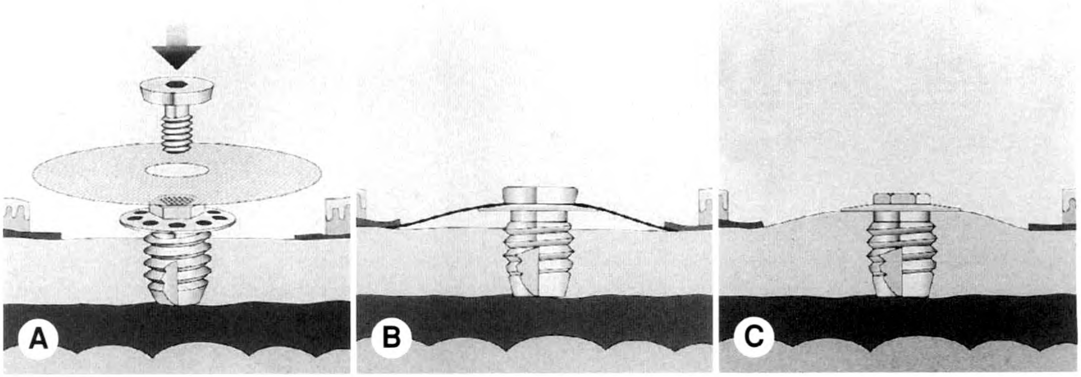


Fig 2. Schematic drawings of principles used for applying expanded polytetrafluoroethylene (e-PTFE) membranes. A) Membrane is applied on top of flange fixture and anchored by cover screw. B) Edges of membrane are covered by periosteum, which is sutured to cover membrane. C) After interval of 4 to 6 months, it can be expected that cortical bone formation will continue under membrane, ideally, up to flange.

to study the possibility of using expanded polytetrafluoroethylene (e-PTFE) membranes in the temporal bone to aid in the insertion of fixtures for osseointegration. The hypothesis at stake was whether guided tissue generation using barrier membranes could promote bone around 4-mm fixtures placed in temporal bones with a thickness of 1 to 2 mm. Second, we wished to establish whether insertion of longer fixtures could compensate for appositional growth of the temporal bone at a later time.

MATERIALS AND METHODS

The protocol used for the study was approved by the ethics committee of Sahlgrenska University Hospital. Ten patients below the age of 10 years who underwent surgery for BAEs or BAHAs between 1993 and 1996 were studied. Bone available preoperatively was measured with computed tomography (CT) scanning of the temporal region. The surgical procedure for implant installation was performed in 2 steps as described by Tjellström,[4] and involved gentle handling of the soft tissue and bone. This concept implies that at the first-stage operation, the skin over the implant site was incised, continuing through the subcutaneous tissue and periosteum. A suitable site for the BAHA was chosen in the temporal line, 50 to 55 mm behind and 30 mm above the external ear canal. For the BAE, 2 implant sites were selected, 20 mm behind the external ear canal and 20 mm apart. The holes were drilled under profuse irrigation with saline solution. We inserted 3.75-mm-diameter threaded flange fixtures of 3- or 4-mm lengths (SEC 001, SEC 002; Nobel Biocare) into the holes. The soft tissue was thereafter sutured and the implants were allowed to integrate in the bone for a period of 4 months. At the second-stage operation, standard titanium abutments for the hearing aid or auricular episthesis (SHCB 179, SEC 007, SEC 008, SEC 010; Nobel Biocare) were adapted on the fixtures, and the skin penetration was prepared as described earlier.[5] Antibiotics were not used at any time during the study.

For installation of e-PTFE membranes, at the time of first-stage surgery, the periosteum was incised and reflected in a 2-cm diameter around the fixture hole. The flange fixtures were inserted with the base in contact with the dura mater, but not penetrating it. The bone thickness in the implant drilling holes was measured with a standardized periodontal probe (Hu-Friedy UNC-15, DAB Dental AB, Gothenburg), as was the distance between the flange and the cortical bone. The measurements were taken from the flange to the longest distance between the flange and the cortical bone. Half the fixtures inserted were covered with e-PTFE membranes (standard e-PTFE membranes; OV4, OV6, Gore & Associates AB WL, Mölndal, Sweden) in a modification of the technique described earlier[6] (Fig 2). The implant chosen for coverage with a membrane was not randomly selected; rather, the fixture that had the worst anchorage was selected to be covered by a membrane. For each individual, 2 fixtures were inserted; 1 of these was covered with a membrane (group A), and the other served as a control (group B). The membranes were individually cut into suitable sizes, adapted on the fixture with the center hole of the fixture in the center of the membrane, and fixed with the cover screw (Fig 3). The periosteal edges were lifted up, and the membrane's edges were applied under the periosteum, after which the periosteal incision was sutured with 5-0 resorbable stitches and the skin was sutured with 6-0 nylon.

The other half of the fixtures were left uncovered (group B). The measurements of the bone thickness and the distance between the cortex and the flange were performed in a similar way. Bone gain was measured clinically at the second-stage procedure in the

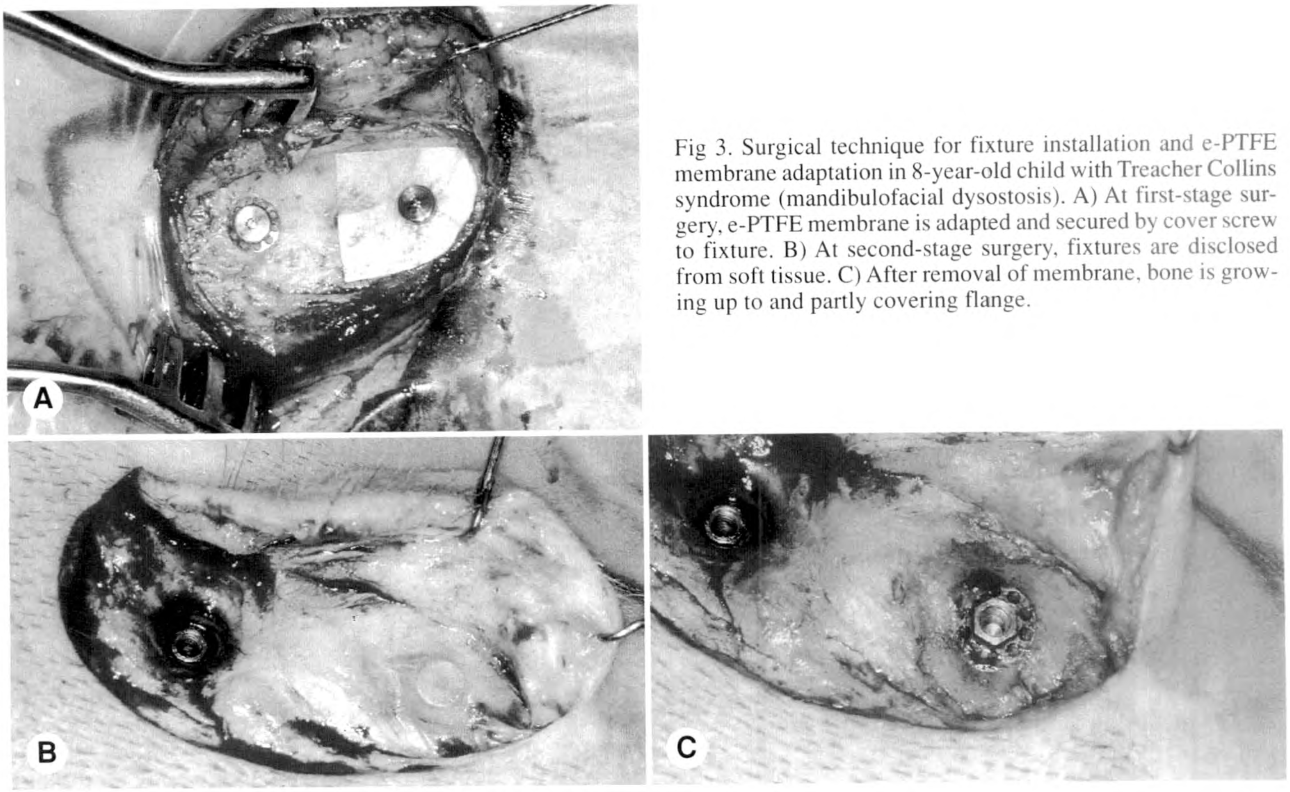


Fig 3. Surgical technique for fixture installation and e-PTFE membrane adaptation in 8-year-old child with Treacher Collins syndrome (mandibulofacial dysostosis). A) At first-stage surgery, e-PTFE membrane is adapted and secured by cover screw to fixture. B) At second-stage surgery, fixtures are disclosed from soft tissue. C) After removal of membrane, bone is growing up to and partly covering flange.

2 groups, 4 months after the first-stage procedure, with the help of the graded probe. As the probe was graded in 1-mm intervals, the distance closest to a half-millimeter was registered.

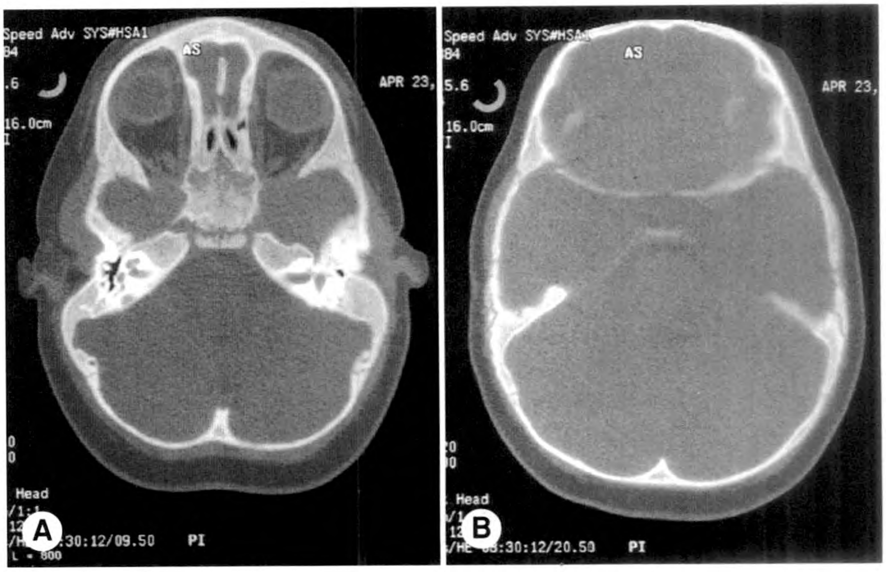
Excess tissue, removed together with the e-PTFE membranes at the second-stage surgery, was immersion-fixed in 10% neutral formalin, decalcified, sectioned in 10-µm-thick sections on a microtome, stained with hematoxylin-eosin, and studied under a light microscope.

All patients that were included in the study had malformed temporal bones. An example of preoperative CT scanning of the temporal bone of a 2-year-old child with Treacher Collins syndrome is shown in Fig 4. As can be seen from this Figure, bone available for implant surgery was, on the left side, approximately 1 mm and, on the right side, 2 mm. For installation of a BAHA, the right side was thus chosen.

RESULTS

Four of the patients had syndromic diagnoses (3 had Treacher Collins syndrome, and 1 had hemifa-

Fig 4. Computed tomography scanning of temporal bones of 2-year-old child with Treacher Collins syndrome (mandibulofacial dysostosis). A) Section at vestibular apparatus level. B) Section in temporal line. As can be seen, thickness of cortical bone available for fixture installation for bone-anchored hearing aid is only approximately 1 mm on left side and 2 mm on right side.



DISTANCE BETWEEN CORTICAL BONE AND FIXTURE FLANGE IN CORRELATION TO LENGTH OF FIXTURE AND COVERAGE WITH E-PTFE MEMBRANE AT FIRST- AND SECOND-STAGE SURGERY

Group A			*Group B*		
Fixture Length	*Stage 1*	*Stage 2*	*Fixture Length*	*Stage 1*	*Stage 2*
3	1.0	0	3	1.0	0.5
3	1.5	0	3	1.0	0
3	1.0	0.5	3	1.5	1.0
3	1.5	0	3	1.0	0.5
3	1.5	0	4	1.5	0.5
3	1.0	0	4	1.0	0
4	1.5	0.5	4	1.5	1.0
4	1.0	0	4	1.5	0.5
4	2.0	0	4	1.0	0
4	1.5	0.5*	4	1.5	0.5
4	2.0	0.5	4	1.5	1.0
4	1.5	0	4	1.0	1.0
4	1.0	0	4	1.5	0.5
4	1.0	0.5*	4	1.0	1.0
4	1.5	0	4	1.5	0.5
4	1.0	0			
4	1.5	0.5			

Data are in millimeters. Group A had coverage with expanded polytetrafluoroethylene (e-PTFE) membrane; group B did not.

*Membrane found to be dislodged at second-stage surgery.

cial microsomia), whereas the other 6 had isolated malformations of the ears without further malformations of the body. There were 6 boys and 4 girls, with a mean age of 7 years, in the study. The youngest child was 2 years old, and the oldest child was 9 years old. The follow-up time after surgery varied from 6 months to 4 years, with a mean of 2.4 years.

Altogether, 32 implants were inserted in the temporal bones, 17 of which were covered with e-PTFE membranes. Twenty-seven of the implants were used for rehabilitating patients with BAEs, and 5 implants were for BAHAs. Ten of the fixtures were 3 mm long, and the other 22 were 4 mm long. The difference in distance between the flange and the cortical bone (bone gain) between the 2 groups is presented in the Table. The bone gain between stage 1 and 2 operations in group A (fixtures covered with e-PTFE membranes) was estimated to be 1.206 ± 0.398 mm. The bone gain between stage 1 and 2 operations in group B (fixtures uncovered) was estimated to be 0.767 ± 0.417 mm. On a statistical comparison between the 2 groups (Student's *t*-test for paired comparisons), the difference between the 2 groups was significant at the p = .004 level.

Two membranes showed damage or dislodgement at the second-stage procedure, with less than optimal bone height. None of the implants were, however, unstable at the second-stage surgery or have so far been lost to follow-up.

Light microscopic findings of tissue removed when the e-PTFE membranes were removed at second-stage surgery are presented in Fig 5. As can be seen from the histologic specimens, lamellar bone was formed under the membranes with evidently vital bone, functioning osteocytes, and developed blood vessels inside the bone lamellae.

DISCUSSION

The use of e-PTFE membranes has been shown to be helpful in clinical as well as experimental dentistry.[6-10] Originally it was used to stimulate regeneration of the periodontium.[11] With time, it has further been used to stimulate bone regeneration around titanium implants used in the maxilla and mandible. Bone gain has been shown to occur horizontally[12] and vertically in the jaws.[13] It has also been shown that bone gain can occur not only in the site of earlier lost bone, but also in areas that should not form bone.[14] The principles of how the barrier membranes function are still under investigation, but theoretically it seems that the basic mechanisms include prevention of fibroblasts migrating into a bony defect, prevention of contact inhibition by heterotopic cell interaction, exclusion of cell-derived soluble inhibitory factors, local concentration of growth stimulatory factors, and stimulatory properties of the membrane itself.[3]

As the principles of guided tissue regeneration seem to work in the mandible and maxilla, it seems reasonable to assume that they could also function in other bones of the body. To the authors' knowledge, there were no earlier studies conducted to find out if bone promotion could be induced by barrier membranes in the temporal bone. Since the obtained bone growth under the barrier membranes is considered to be new bone formation and not regrowth of bone into an obtained defect, we have in this study used the term guided bone *generation*, and not regeneration.

The principal clinical problem in the malformed temporal bone is a relative lack of bone suitable for implant surgery. There could be several ways to solve this problem. One solution could be to graft bone to the region of implant installation. A reasonable donor site would then be the calvarium, as surgery is taking place in the same region. The immediate problem one then encounters regarding the malformed child is that the relative lack of appropriate bone is not restricted to the temporal bone, but is often general in the calvarium. One would then have to make further incisions (and scars) to obtain a reasonable

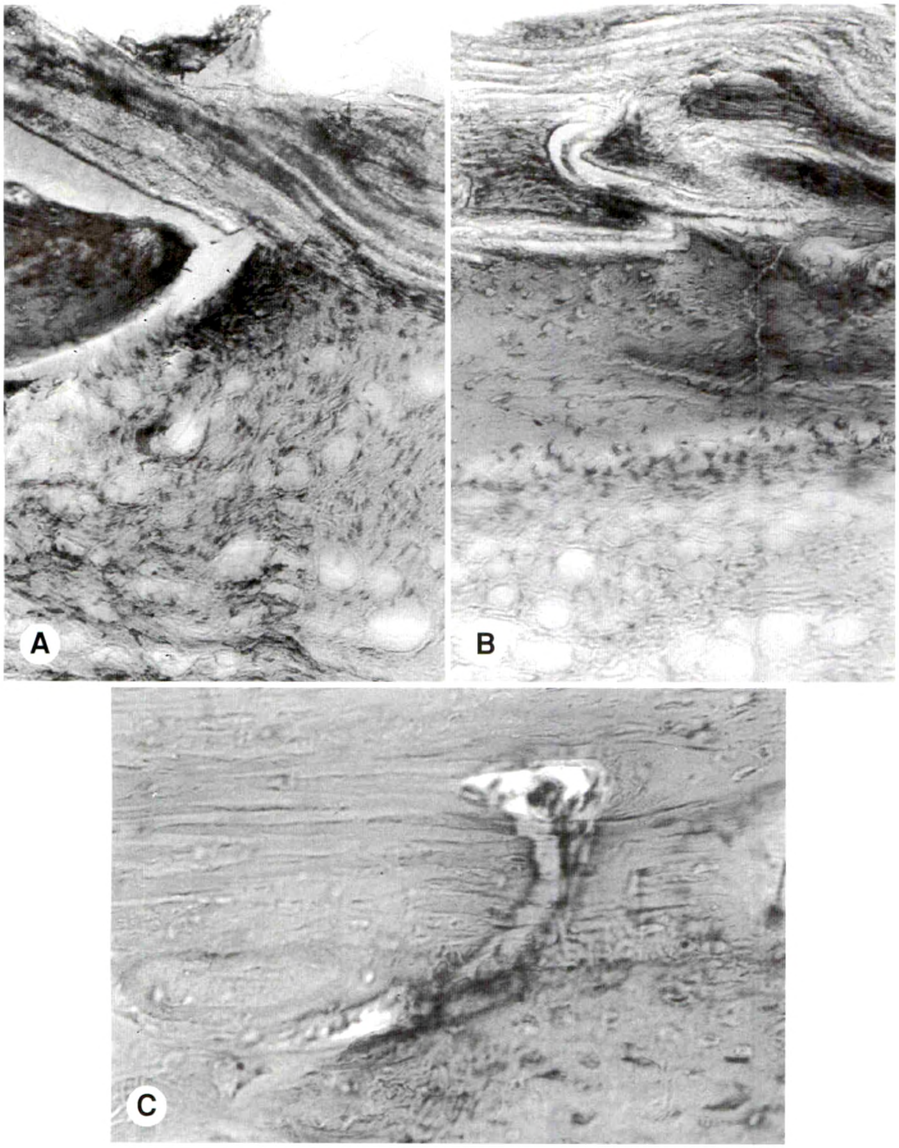


Fig 5. Histologic micrographs of excess tissue removed from temporal bone of 8-year-old child with isolated ear malformation. A) Region of periosteum covering e-PTFE membrane, where membrane is visible, as is newly formed lamellar bone (H & E, original ×10). B) Region of membrane below which lamellar bone is formed (H & E, original ×10). C) In higher magnification, it can be seen that bone is of lamellar type, with vital osteocytes and blood vessels inside bone (H & E, original ×25).

amount of bone. Other donor sites could be the tibia, fibula, iliac crest, mandible, etc, but for the same reasons, extra incisions might be contraindicated, if only for psychological reasons. Other grafting techniques such as the use of hydroxylapatite could be used to promote hard tissue for prosthetic devices or implant surgery.[15] We decided not to use alloplastic materials in this study, as basic knowledge of how such a material functions in the growing temporal bone is lacking. Rather, the use of a bone-promoting material that could be removed at second-stage surgery was attractive.

One of the problems one has to face when inserting implants in the young temporal bone is the continuous growth of the bone. The temporal bone is generally increasing in size after birth by appositional growth. As an implant inserted in a growing bone will become ankylotic,[16] its position in the bone will with time become deeper. Clinically, this tendency is recognized as a reduced distance from the skin to the bone. We have corrected for this shorter distance in 2 ways. The first way is to exchange the abutment for a longer one. This is mainly applicable in patients with BAEs, in which abutments of different lengths can be obtained. As the abutment for the BAHA is of standard length, the other option is to reduce the soft tissue and bone around the implant. This can be done as an outpatient procedure, making a skin incision, lifting a skin flap, and at the same time reducing the thickness of the skin flap. The bone is then thinned with a round bur until the flange of the fixture is visible again. This has seldom been necessary to do more than 2 or 3 times in one person during the complete growth period.

One advantage to using the barrier membrane technique is that the implant can be placed more externally, and hence in a position to partly compensate for the appositional growth of the temporal bone.

The ideal position for compensating for all the appositional growth of childhood is not yet established, but would probably require longer implants than the 4-mm fixtures available today.

No radiologic control of bone generation was used in this study for several reasons. At present, there is no simple technique available by which one could estimate bone growth around implants in a longitudinal way in the temporal bone. One therefore has to rely on CT techniques, which, aside from being expensive, contribute a substantial radiation dose to the region. As several disciplines are involved in the rehabilitation of the malformed child, during this person's lifetime one would assume that the total radiation dose to the temporal bones would be considerable.

The obtained bone under the membranes was estimated to be approximately 1.2 mm over a 4-month period. As the membranes were kept in place by the cover screw, one would estimate that if other types of membranes (dome-shaped) were used, which are held in place by, for example, titanium mesh, more bone could be formed. In a study by Becker et al,[9] there was an average of 4 to 4.8 mm of bone growth over a 6-month period. Probably, an increased time (more than the 4 months we used) to second-stage surgery would also increase the bone formation under the membrane.

Dehiscence of the membranes seems to be an oral clinical as well as an experimental problem. In a clinical study by Wachtel et al,[8] dehiscences occurred in the central part of the surgically created flaps, and indicated a restricted microvascular supply. The possibility that microorganisms might invade the porous structure of the membranes was also suggested as an explanation for tissue dehiscence.[8] We have not experienced any dehiscences of the membranes in this limited clinical study. The probable reason for this is that the implants are not loaded at any time before second-stage surgery. The skin flap is relatively thicker than the mucosal flap obtained in the oral cavity. One would also estimate that the vascularity of the relatively young patient is sufficient to promote normal healing in the temporal region.

CONCLUSION

It is concluded that the use of guided tissue generation in the temporal bone might be a helpful tool for obtaining enough bone to support proper fixture installation.

REFERENCES

1. Granström G, Tjellström A. The bone-anchored hearing aid (BAHA) in children with auricular malformations. Ear Nose Throat J 1997;76:238-47.

2. Jacobsson M, Albrektsson T, Tjellström A. Tissue-integrated implants in children. Int J Pediatr Otorhinolaryngol 1992;24:235-43.

3. Dahlin C. Scientific background of guided bone regeneration. In: Buser D, Dahlin C, Schenk RK, eds. Guided bone regeneration in implant dentistry. Chicago, Ill: Quintessence Publishing, 1994:31-48.

4. Tjellström A. Other applications of osseointegrated implants. In: Brånemark P-I, Zarb G, Albrektsson T, eds. Tissue-integrated prostheses. Osseointegration in clinical dentistry. Chicago, Ill: Quintessence Publishing, 1985:333-44.

5. Tjellström A. Osseointegration systems and their applications in the head and neck. Adv Otolaryngol Head Neck Surg 1989;3:39-70.

6. Becker W, Becker BE. Bone promotion around e-PTFE–augmented implants placed in immediate extraction sockets. In: Buser D, Dahlin C, Schenk RK, eds. Guided bone regeneration in implant dentistry. Chicago, Ill: Quintessence Publishing, 1994:137-54.

7. Zablotsky M, Meffert R, Caudill R, Evans G. Histological and clinical comparisons of guided tissue regeneration on dehisced hydroxylapatite-coated and titanium endosseous implant surfaces: a pilot study. Int J Oral Maxillofac Impl 1991; 6:294-303.

8. Wachtel HC, Langford A, Bernimoulin J-P, Reichart P. Guided bone regeneration next to osseointegrated implants in humans. Int J Oral Maxillofac Impl 1991;6:127-35.

9. Becker W, Dahlin C, Becker BE, et al. The use of e-PTFE barrier membranes for bone promotion around titanium implants placed into extraction sockets: a prospective multicenter study. Int J Oral Maxillofac Impl 1994;9:31-40.

10. Becker W, Lekholm U, Dahlin C, Becker BE, Donath K. The effect of clinical loading on bone regeneration by GTAM barriers: a study in dogs. Int J Oral Maxillofac Impl 1994;9:305-13.

11. Nyman S, Lindhe J, Karring T. Reattachment–new attachment. In: Lindhe J, ed. Textbook of clinical periodontology. 2nd ed. Copenhagen, Denmark: Munksgaard, 1989:450-76.

12. Dahlin C, Andersson L, Linde A. Bone augmentation at fenestrated implants by an osteopromotive membrane technique. A controlled clinical study. Clin Oral Impl Res 1991;2:159-65.

13. Dahlin C, Lekholm U, Linde A. Membrane-induced bone augmentation at titanium implants. A report on ten fixtures followed from 1 to 3 years after loading. Int J Period Restor Dent 1991;11:273-81.

14. Linde A, Thorén C, Dahlin C, Sandberg E. Creation of new bone by an osteopromotive membrane technique. J Oral Maxillofac Surg 1993;51:892-7.

15. Kent JN, Quinn JH, Zide MF, Guerra LR, Boyne PJ. Alveolar ridge augmentation using nonresorbable hydroxylapatite with or without autogenous cancellous bone. J Oral Maxillofac Surg 1983;41:629-36.

16. Ödman J, Gröndahl K, Lekholm U, Thilander B. The effect of osseointegrated implants on the dento-alveolar development. A clinical and radiographic study in growing pigs. Eur J Orthod 1991;13:279-86.

Ann Otol Rhinol Laryngol 108:1999

ENDOSCOPIC SINUS SURGERY IMPROVES PULMONARY FUNCTION IN PATIENTS WITH ASTHMA ASSOCIATED WITH CHRONIC SINUSITIS

KATSUHISA IKEDA, MD
NORIKO TANNO, MD
GEN TAMURA, MD
HIDEAKI SUZUKI, MD
TAKESHI OSHIMA, MD
AKIRA SHIMOMURA, MD
SEIICHIRO NAKABAYASHI, MD
TOMONORI TAKASAKA, MD
SENDAI, JAPAN

We evaluated the clinical efficacy of endonasal endoscopic sinus surgery (ESS) in patients with asthma associated with chronic sinusitis. Twenty-one patients (13 men and 8 women) from 27 to 72 years old were enrolled in this study. All patients had had sinus-related symptoms for more than 3 months and had computed tomographic evidence of paranasal sinus opacification. Fifteen patients underwent bilateral endonasal ESS under local anesthesia, and 6 other patients without surgery were controls. The sinus-related symptoms of the preoperative and postoperative periods were assessed via a questionnaire. The period 6 months prior to surgery was compared with that 6 months postoperatively with regard to peak expiratory flow and total dosage of systemic glucocorticoids. Sinus-related symptoms in the ESS group were significantly improved 6 months postoperatively. The average peak expiratory flow 6 months following surgery was improved in the ESS patients, ranging from 40 to 190 L/min. Seven patients showed a reduction in the need for corticosteroids, whereas 2 patients were unchanged and 2 patients required larger dosages. The remaining 4 patients needed no corticosteroids before or after ESS. No significant changes in sinus-related symptoms or peak expiratory flow were obtained for the control group. Improvement of paranasal sinus disease by successful ESS can alleviate pulmonary dysfunction in asthma associated with chronic sinusitis. We believe that adequate and positive treatment for chronic sinusitis would reduce not only the nasal and sinus-related symptoms evoked by chronic sinusitis, but also some of the signs induced by asthma.

KEY WORDS — asthma, corticosteroid, endoscopic sinus surgery, expiratory peak flow.

INTRODUCTION

Close relationships exist between the upper and lower respiratory tracts.[1] It is well known that chronic sinusitis coexists in as many as 40% to 75% of patients with asthma.[2-4] Many patients with lower respiratory tract disease have a history indicating that chronic sinusitis preceded the development of inflammatory diseases of the lower respiratory tract.[1,5] Although clinical evidence is accumulating that chronic sinusitis exacerbates lower airway disease, more direct and objective studies are needed to elucidate the important role that chronic sinusitis may play in lower airway disease. Direct evidence of an association could be obtained by examining the effect of treatment of chronic sinusitis on pulmonary symptoms and function. Appropriate medical treatment for chronic sinusitis has been reported to have a beneficial effect on asthma symptoms.[6-8] Surgical management of chronic sinusitis has also been found to improve pulmonary function and symptoms.[5,9-12]

Endoscopic sinus surgery (ESS) has been widely accepted as the primary surgical modality for the treatment of chronic sinusitis. The concept of this technique is based on the changes in the mucociliary function and mucosal disease[13,14] that can be brought about by removal of the pathologic condition in the middle meatus–anterior ethmoid complex–maxillary ostium and by reestablishment of physiological ventilation and drainage in the paranasal sinuses.[15] In addition to the symptomatic improvement,[14,16] ESS provides a significant improvement in the diseased areas of the paranasal sinuses, as revealed by computed tomography (CT) scans, nasal endoscopy, quantitative olfactory acuity, and nasal patency.[17-20] Although a few reports have mentioned an amelioration of asthma after ESS, changes in objective pulmonary function have not yet been well documented. The present study focuses on the benefits of ESS on pulmonary function in asthma on the basis of more objective criteria.

MATERIALS AND METHODS

Twenty-two patients consecutively underwent initial bilateral ESS from April 1992 to May 1994 at Tohoku University School of Medicine. Five patients were excluded because they did not perform a daily pulmonary function test after surgery. Another 2 patients were excluded because they were not followed up after surgery. There were 10 men and 5 women from 27 to 72 years old (mean 47 ± 14 years). The 6

From the Departments of Otorhinolaryngology (Ikeda, Tanno, Suzuki, Oshima, Shimomura, Nakabayashi, Takasaka) and 1st Internal Medicine (Tamura), Tohoku University School of Medicine, Sendai, Japan.

CORRESPONDENCE — Katsuhisa Ikeda, MD, Dept of Otorhinolaryngology, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-0872, Japan.

control subjects (mean age 42 years; range 32 to 64 years; 3 men and 3 women) had received diagnoses of asthma associated with chronic sinusitis and had not given informed consent for ESS but used intranasal corticosteroid spray alone. In the control subjects, the study started at the time of the diagnosis of asthma associated with chronic sinusitis and was followed by a 1-year follow-up.

Chronic sinusitis was diagnosed by the presence of sinus-related symptoms lasting for more than 3 months and opacification of paranasal sinuses as revealed by coronal CT scans. The presence of nasal discharge, postnasal drainage, and nasal obstruction was recorded and their severity was defined as follows: severe 3, moderate 2, slight 1, and absence of symptoms 0. Patients were asked to complete questionnaires about the above-mentioned symptoms preoperatively and in the postoperative follow-up. The extent of disease was quantitated by a scoring system for CT scans according to a previous study.[20] Based on the degree of opacification of coronal views, scores of 0 to 3 (80% to 100% opacification = 3; 50% to 80% = 2; 20% to 50% = 1; less than 20% = 0) were assigned for each sinus (2 frontal, 2 maxillary, 2 ethmoid, 2 sphenoid) and 2 ostiomeatal complex units. A total of 30 was possible.

The diagnosis of asthma was based on the definition of the American Thoracic Society. Intradermal skin testing was performed with common inhalant allergens. The total serum immunoglobulin E (IgE) and specific serum IgE against common inhalant allergens were also determined. Atopic status, which was defined as having 1 or more positive skin reactions and/or more than 250 units of total serum IgE, was found in 6 of the 21 patients (29%). All patients were treated with bronchodilators, including theophylline, ß-adrenergics, and inhaled corticosteroids, in the same manner and to the same extent after surgery as before.

Pulmonary function and systemic corticosteroid medication were compared between the preoperative and postoperative periods. Each patient was assessed for peak expiratory flow 3 times daily according to the National Asthma Education Program.[21] The peak expiratory flow was measured with Personal Best (Healthscan Products Inc, Cedar Grove, NJ) from 6 months preoperatively to 6 months postoperatively. Since the airway caliber in patients with asthma shows seasonal variation, the measurements of the peak expiratory flow were performed before and after surgery for only 1 month, each in the same month. The total dosage of systemic corticosteroids (dexamethasone sodium phosphate) administered 6 months before and after surgery was calculated.

The ESS was performed according to Kennedy et al[13] and Stammberger.[14] Surgery in all cases was performed under local anesthesia. Briefly, infundibulotomy was first performed whereby the medial infundibular wall was removed with a sickle knife. The uncinate process was then subluxated medially and removed with forceps. The anterior ethmoid cells and ethmoid bulla were removed with forceps. The posterior ethmoid and sphenoid sinuses could be evacuated step by step when necessary. Finally, the maxillary ostium was identified visually with a 30° or 70° telescope. The obstructed opening in severe cases was widened with a curette and a back-biting forceps into the anterior and posterior fontanelles. Severely inflamed and polypoid mucosa or polyps found in the maxillary sinus were removed by curved forceps or vaporized by a potassium titanyl phosphate 532 laser. Polypoid degeneration around the olfactory fissure was meticulously removed by forceps, and the olfactory fissure was opened as widely as possible. The nasal cavity was packed for 5 to 7 days with gauze coated with poly-*N*-acetyl glucosamine (Beschitin F, Morishita-Rusel Pharmacy, Osaka, Japan). Postoperative cleaning of blood and fibrin clots from the operative cavity was meticulously performed daily on postoperative days 5 to 10 and then weekly for 1 to 2 months, and once every 1 or 2 months thereafter. Most of the patients received oral antibiotics, usually cefaclor (750 mg daily), for 1 week postoperatively. After that, intranasal corticosteroid spray was administered for postoperative management.

Results were expressed as mean ± standard deviation and were compared with a paired *t*-test; a p value of less than .05 was recognized as significant.

RESULTS

The average scores of initial symptoms in the ESS and control groups were 5.8 ± 1.6 and 6.2 ± 1.7, respectively, showing no significant difference. Further, the mean CT score was comparable for both groups (13 ± 7 in the ESS group versus 11 ± 9 in the control group). Total scores of each sinus-related symptom were apparently and promptly decreased in the ESS group 3 months postoperatively, and the decrease continued to 6 months postoperatively (Fig 1). The average improvement rate in the scores was 71% ± 27% 3 months and 86% ± 13% 6 months after surgery, showing a significant improvement in each period. On the other hand, control patients did not show any improvement (improvement rate 9% ± 15%) at the 6-month follow-up.

The average peak expiratory flow following ESS was improved in all patients, ranging from 40 to 190

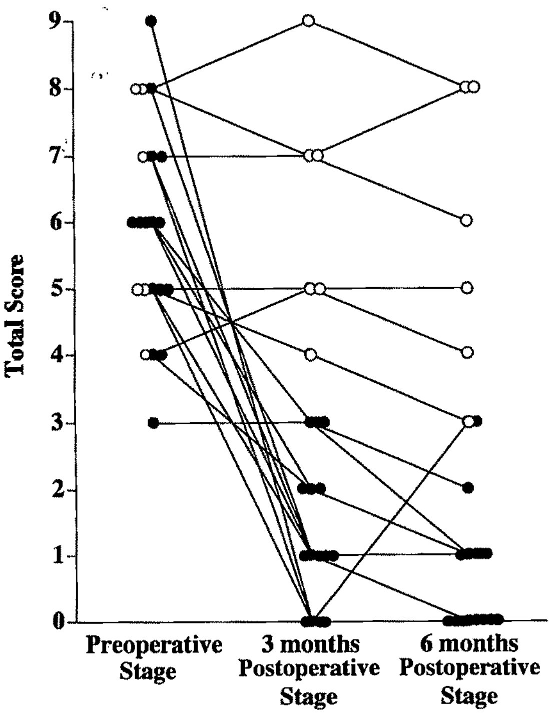


Fig 1. Time course of total scores of sinus-related symptoms in each patient. Closed circles — patients after surgery; open circles — controls.

L/min (Fig 2). A significant increase (98 ± 45 L/min, $p < .005$) in the average peak expiratory flow following ESS was recognized. No significant difference in improvement of the peak expiratory flow between the presence (27% ± 17% improvement, n = 4) and absence (26% ± 16% improvement, n = 11) of atopy was recognized. In contrast, there was no significant change in the peak expiratory flow during the 1-year follow-up in control patients, which corresponded to 115% ± 35% of the initial value.

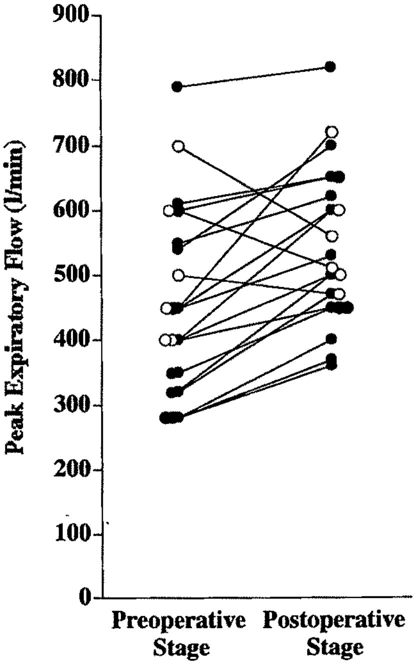


Fig 2. Changes in peak expiratory flow in each patient. Closed circles — patients after surgery; open circles — controls.

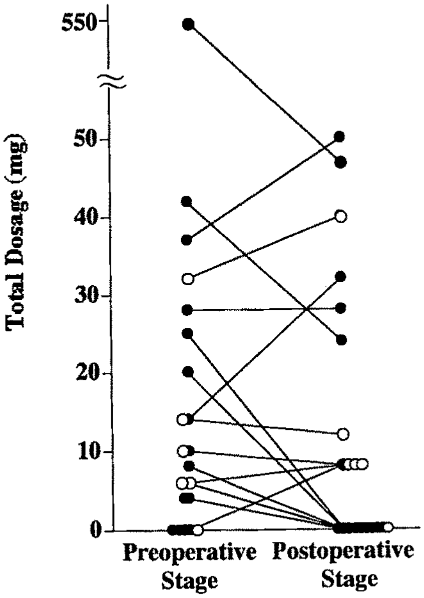


Fig 3. Comparison of systemic corticosteroid requirements between preoperative and postoperative periods in each patient. Closed circles — patients after surgery; open circles — controls.

Four patients were well controlled, without severe asthma episodes (ie, episodes requiring intermittent administration of systemic corticosteroids) before or after ESS. The other 11 patients required intermittent bursts of systemic corticosteroids. Although 6 patients no longer required systemic corticosteroids after ESS, 2 patients required larger doses of systemic corticosteroids postoperatively than preoperatively (Fig 3). One patient showed a remarkable decrease in corticosteroid dosage. The total dosage was unchanged in the remaining 2 patients. There was no significant change in the total dosage of systemic corticosteroids between the preoperative and postop-

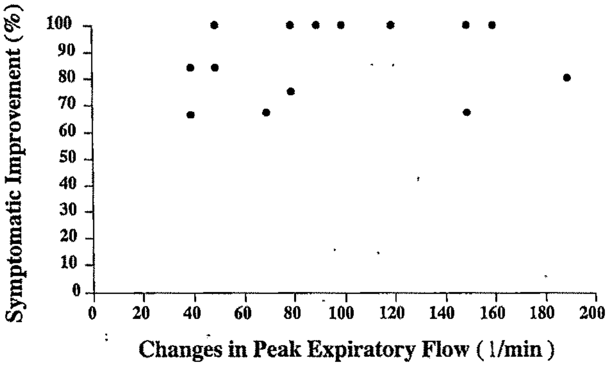


Fig 4. Relationship between improvement rate of sinus-related symptoms and increase in average peak expiratory flow following endoscopic sinus surgery.

erative periods in the 11 patients requiring systemic corticosteroids. In controls, no significant change in dosage was obtained.

The relationship between the improvement rate of sinus-related symptoms and the increase in the average peak expiratory flow following ESS was examined (Fig 4), but there was no correlation ($r = .197$, $p > .02$, Spearman's rank correlation).

DISCUSSION

The present study revealed a significant improvement in pulmonary function of patients with asthma associated with chronic sinusitis following ESS. The peak expiratory flow correlates well with forced expiratory volume in 1 second,[22,23] one of the accepted parameters for evaluating the severity of obstructive conditions of the airway. In contrast, several investigators have mentioned that the peak expiratory flow is not really an adequate measure of lung function per se. However, because of seasonal and daily variation of the airway caliber in asthmatic patients, the average peak expiratory flow for only 1 month, in the same month, preoperatively and postoperatively, rather than spirometric parameters, was adopted as a practical and convenient pulmonary function test in the present study. Mings et al[5] reported significant improvements in pulmonary function scores in 5 patients at 5 years following bilateral intranasal sphenoethmoidectomy. However, the beneficial effects of ESS on objective pulmonary function scores have not yet been determined. Nishioka et al[10] revealed a reduction of corticosteroid medication following ESS, but did not use any objective pulmonary function tests. Manning et al[12] failed to find a significant change in pulmonary function scores in pediatric patients with asthma. The effect of postoperative topical application of corticosteroids to the nasal cavity in asthma remains undetermined. However, no clinical efficacy was obtained in our control patients receiving intranasal corticosteroid spray alone, and this finding suggests that the spray made little contribution to sinus or bronchial disease. Thus, the present study is the first to support that ESS has a beneficial effect in adult asthma associated with chronic sinusitis on the basis of objective pulmonary function tests. Further, the findings suggest that improvement in paranasal sinus disease leads to an alleviation of asthma, suggesting an association between sinusitis and asthma.

Previous reports[10,12] suggesting that the required dosage of corticosteroids was significantly decreased following ESS are inconsistent with the present study. This discrepancy may have resulted from the fact that the present group included steroid-dependent patients and that the follow-up period of 6 months before and after surgery is not sufficient to eliminate seasonal effects on asthmatic conditions. Further study is required for elucidating this point.

The pathophysiological mechanisms by which sinusitis can trigger asthma are still unknown. However, a recent hypothesis[8,24,25] is that inflammatory mediators produced in the paranasal sinuses elicit bronchoconstriction, either by stimulating neural receptors in the nose, sinuses, or pharynx or by dripping into the lower airway. This hypothesis was confirmed by a series of experiments with an animal model of sinusitis,[24] indicating that nonspecific bronchial hyperresponsiveness is sustained by activation of a pharyngobronchial reflex, rather than by a nasobronchial reflex or by seeding of the inflammatory process into the lower airway. In addition to animal experiments, the results of clinical investigations[8,25] support this hypothesis. Although in the present study the improvement of the sinus-related symptoms was not correlated with that of pulmonary function, worsening of the sinus-related symptoms tended to worsen the peak expiratory flow on long-term follow-up (data not shown).

In conclusion, elimination of paranasal sinus disease by ESS can alleviate pulmonary dysfunction in asthma associated with chronic sinusitis. We believe that adequate and positive treatment for chronic sinusitis will reduce not only nasal and sinus-related symptoms evoked by chronic sinusitis, but also some of the signs induced by asthma.

REFERENCES

1. Slavin RG. Relationship of nasal disease and sinusitis to bronchial asthma. Ann Allergy 1982;49:76-80.

2. Berman S, Mathison DA, Stevenson DD, Usselman JA, Shore S, Tan EM. Maxillary sinusitis and bronchial asthma: correlation of roentgenograms, cultures and thermograms. J Allergy Clin Immunol 1974;53:311-8.

3. Katz R, Rachelefsky G, Goldberg M, et al. Sinusitis in children with respiratory allergy. J Allergy Clin Immunol 1978; 61:190-5.

4. Sircar M, Karol RK, Bhatia P. Radiological abnormalities of paranasal sinuses in asthmatics. with rhinitis. Am J Rhinol 1995;9:99-101.

5. Mings R, Friedman WH, Linford P, Slavin RG. Five year follow-up of the effects of bilateral intranasal sphenoethmoidectomy in patients with sinusitis and asthma. Am J Rhinol 1988;2:123-32.

6. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive disease in children. Pediatrics 1984;73:526-9.

7. Friedman R, Ackerman M, Wald E, Casselbrant M, Fri-

day G, Fireman P. Asthma and bacterial sinusitis in children. J Allergy Clin Immunol 1984;74:185-9.

8. Bucca C, Rolla G, Scappaticci E, et al. Extrathoracic and intrathoracic airway responsiveness in sinusitis. J Allergy Clin Immunol 1995;95:52-9.

9. Phipatanakul CS, Slavin RG. Bronchial asthma produced by paranasal sinusitis. Arch Otolaryngol 1974;100:109-12.

10. Nishioka GJ, Cool PR, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol Head Neck Surg 1994;110:494-500.

11. Parsons CDS, Phillips CSE. Functional endoscopic surgery in children: a retrospective analysis of results. Laryngoscope 1993;103:899-903.

12. Manning SC, Wasserman RL, Silver R, Phillips DL. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. Arch Otolaryngol Head Neck Surg 1994;120:1142-5.

13. Kennedy DW, Zinreich SJ, Rosenbaum AE, Johns ME. Functional endoscopic sinus surgery: theory and diagnosis. Arch Otolaryngol 1985;111:576-89.

14. Stammberger H. Endoscopic endonasal surgery — concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiological considerations. Otolaryngol Head Neck Surg 1986;94:143-7.

15. Ikeda K, Oshima T, Furukawa M, et al. Restoration of the mucociliary clearance of the maxillary sinus following endoscopic sinus surgery. J Allergy Clin Immunol 1997;99:48-59.

16. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. Laryngoscope 1990; 100:79-84.

17. Lund VJ, Holmstrom M, Scadding GK. Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. J Laryngol Otol 1991;105:832-5.

18. Yamagishi M, Hasegawa S, Suzuki S, Nakamura H, Nakano Y. Effect of surgical treatment of olfactory disturbance caused by localized ethmoiditis. Clin Otolaryngol 1989;14:405-9.

19. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. Laryngoscope 1992;102(suppl 57).

20. Ikeda K, Kondo Y, Sunose H, et al. Subjective and objective evaluation in endoscopic sinus surgery. Am J Rhinol 1996; 10:217-20.

21. National Heart, Lung, and Blood Institute. Statement on technical standards for peak flow meters. National Asthma Education Program, Expert Panel Report, November 14, 1990.

22. Wright BM, McKerrow CB. Maximum forced expiratory flow rate as a measure of ventilatory capacity. BMJ 1959;2: 1041-7.

23. Vaughan TR, Weber CRW, Tipton WR, Nelson HS. Comparison of PEFR and FEV_1 in patients with varying degrees of airway obstruction. Effect of modest altitude. Chest 1989;95: 558-62.

24. Irvin CG. Sinusitis and asthma: an animal model. J Allergy Clin Immunol 1992;90:521-33.

25. Bucca C, Rolla G, Brussino L, de Rose V. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? Lancet 1995;346:791-5.

Ann Otol Rhinol Laryngol 108:1999

DOUBLE-BLIND COMPARATIVE TRIAL OF CIPROFLOXACIN VERSUS CLARITHROMYCIN IN THE TREATMENT OF ACUTE BACTERIAL SINUSITIS

KEVIN CLIFFORD, MD
BOISE, IDAHO

WERNER HUCK, MS
SALT LAKE CITY, UTAH

MICHAEL SHAN, PHD
WEST HAVEN, CONNECTICUT

ROBERT TOSIELLO, MS
WEST HAVEN, CONNECTICUT

ROGER M. ECHOLS, MD
WEST HAVEN, CONNECTICUT

ALLEN HEYD, PHD
WEST HAVEN, CONNECTICUT

AND THE SINUSITIS INFECTION STUDY GROUP

This multicenter, randomized, double-blind trial compared the efficacy and safety of ciprofloxacin (CIP; 500 mg twice daily for 10 days, placebo for 4 days) to those of clarithromycin (CLARI; 500 mg twice daily for 14 days) in 560 adults with clinically documented and radiologically confirmed acute sinusitis. Of 457 efficacy-valid adults (236 CIP, 221 CLARI), clinical resolution plus improvement at the end of therapy was 84% for CIP-treated patients compared to 91% of CLARI recipients (CI_{95} = –0.131, –0.013). At the 1-month follow-up, more than twice as many CLARI-treated patients, 18 (10%), experienced a relapse, compared to 7 (4%) CIP-treated patients. The combined clinical response analyses (end of therapy and 1-month follow-up) demonstrated that CIP and CLARI were statistically equivalent (CI_{95} = –0.106, 0.044). Diarrhea, nausea, headache, and dizziness were the most frequently reported drug-related adverse events in both treatment groups; diarrhea and taste perversion were reported more frequently among CLARI recipients. In summary, the combined end of therapy and follow-up clinical evaluation analyses revealed that CIP and CLARI were equally effective in the management of acute sinusitis, although twice as many relapses were reported among CLARI recipients.

KEY WORDS — acute bacterial sinusitis, ciprofloxacin, clarithromycin.

Acute documented or suspected bacterial sinusitis in adults is a common clinical infection that is defined as inflammation of the sinuses associated with symptoms and signs lasting 4 weeks or less. It is estimated that physicians in the United States diagnose at least 30 million cases of sinusitis annually.[1,2] Acute sinusitis frequently is a complication of the common cold or another viral infection of the upper respiratory tract.[3] The most common symptoms of acute sinusitis include nasal and postnasal purulent discharge and facial pain over the affected sinus that worsens with movement or percussion, although clinical manifestations are highly variable.[4] Other objective localizing studies, such as radiography, may be desirable to support clinical findings such as fever, headache, malar tenderness, and nasal discharge, which are often nonspecific.

Although the paranasal sinuses are usually sterile, transient colonization by upper respiratory tract bacterial flora can occur, especially when the ciliated epithelia are immobilized by cohabiting viruses.[4,5] Acute bacterial maxillary sinusitis in adults is estimated to be caused by *Haemophilus influenzae* and *Streptococcus pneumoniae* in approximately 50% to 65% of cases.[4-6] While *Moraxella catarrhalis*, *Staphylococcus aureus*, and other streptococcal species (eg, *Streptococcus pyogenes*) are isolated less often in acute sinusitis (10% to 20%), they are found more commonly in patients with recurrent or chronic sinusitis.[6,7] Sinusitis due to anaerobes (eg, *Bacteroides*, *Peptostreptococcus*, or *Fusobacterium* species) accounts for a small proportion of cases and is often associated with dental infections.

Untreated or inadequately treated episodes of acute sinusitis may result in chronic sinusitis due to irreversible changes in the mucosal lining of the sinus. Further, due to their anatomic location and rich vascular supply, sinus infections are potentially life-threatening and may cause intracranial suppurative complications such as epidural or subdural empyema, brain abscess, or cavernous sinus thrombosis.[3,4] Therefore, early diagnosis and appropriate antimicrobial therapy are important for the prevention of suppurative complications and chronic sinusitis. Empiric antimicrobial therapy for acute sinusitis has included ß-lactams, trimethoprim-sulfamethoxazole, and, recently, clarithromycin (CLARI). These agents, to various degrees, provide coverage for the most common organisms implicated in acute sinus infections, including *H influenzae*, *S pneumoniae*, *M catarrhalis*, and *S au-*

This work was supported by a research grant from Bayer Corporation, Pharmaceutical Division, West Haven, Connecticut.

Presented in part at the American College of Allergy and Asthma Immunology 1997 Annual Meeting, San Diego, California, November 8-9, 1997.

CORRESPONDENCE — Werner Huck, MS, Advanced Clinical Research, 34 South 500 East, Suite 102, Salt Lake City, UT 84102.

reus. The optimal prescribed antimicrobial for sinusitis should also have reasonable sinus fluid and tissue concentrations and excellent safety and tolerability, in addition to broad-spectrum microbiological activity.

Several studies have determined that ciprofloxacin (CIP) achieves high maxillary tissue and sinus secretion concentrations. Following multiple 500-mg twice-daily doses in 24 patients with chronic sinusitis, CIP concentrations in sinus mucosa tissue were several-fold higher (2.5 to 8.2 mg/mL) than serum levels (0.8 to 5.0 mg/mL; data on file, Bayer Corporation). In a second study, mean CIP nasal secretion concentrations ranged from 0.04 to 0.27 mg/mL at 2, 5, and 8 hours following the last dose in 5 healthy patients administered 750 mg of oral CIP twice daily for 2 days. These concentrations greatly exceed the MIC90 for commonly encountered sinusitis pathogens.[8] Ciprofloxacin is currently indicated for treatment of acute sinusitis, and published clinical data suggest overall effectiveness of 75% to 95% for patients with acute or chronic sinusitis.[9-15] In a large, multicenter study, a 10-day course of oral CIP (500 mg twice daily) was reported to be as effective as cefuroxime axetil (250 mg twice daily for 10 days) among 453 efficacy-valid patients; resolution or improvement was reported in 87% versus 83% of CIP and cefuroxime patients, respectively.[16] Further, bacteriologic eradication was reported in 97% of CIP-treated and 95% of cefuroxime-treated patients.

Clarithromycin, a new semisynthetic macrolide antibiotic, is indicated for the treatment of acute maxillary sinusitis due to *S pneumoniae*. Limited data are available regarding CLARI's tissue distribution characteristics into respiratory tract tissues. At least 1 study has shown that CLARI concentrates in nasal mucosa with concentrations 6 to 20 times that of serum.[17] The efficacy and safety of CLARI (500 mg twice daily for 14 days) have been demonstrated in 2 sinusitis studies; CLARI was found in both studies to be as effective, both clinically and bacteriologically, as amoxicillin.[18,19]

The present study was undertaken to compare the efficacy and safety of a 10-day oral treatment course of CIP to those of 14-day therapy with CLARI for the management of adults with acute maxillary sinusitis or acute exacerbations of chronic sinusitis.

PATIENTS AND METHODS

Adults with a primary diagnosis of clinically and radiologically documented acute sinusitis of ≤4 weeks' duration were enrolled. Eligible adults, of both sexes, were at least 18 years of age and presented with clinical signs and symptoms of acute sinusitis and radiographs (Waters' view occipitomental position) confirming maxillary sinusitis (ie, air fluid levels, opacification, or ≥6 mm of mucosal thickening). In addition, at least 2 of the following findings consistent with sinus infection were required for study entry: fever (>38°C); leukocytosis (white blood cell count of >10,000/mm^3); symptoms consistent with sinus infection (ie, fever, frontal headache, nasal congestion, postnasal drainage, frequent coughing or throat clearing); or physical findings (ie, malar tenderness, edema).[20] Excluded from the study were patients with any of the following characteristics: inability to take oral medications; hypersensitivity to carboxyquinolones or macrolide-like agents; symptoms for >4 weeks (chronic sinusitis) or frequent recurrent acute sinusitis infections (ie, >2 episodes within last 6 months); unwillingness to undergo a sinus aspiration procedure; known or suspected bacteremia or meningitis; need for concomitant antibacterial agents during the study period; previous enrollment in this study; pregnancy or lactation; or a baseline serum creatinine of ≥3.0 mg/dL. Other exclusion criteria were the administration of an antimicrobial agent within 5 days of study enrollment unless the patient was a treatment failure or had received only 1 or 2 doses of the antibiotic, or the coadministration of terfenadine (Seldane) or astemizole (Hismanal) during the study period. Use of adjunctive measures such as phenylephrine nose drops (0.25% or 0.5%) or oxymetazoline spray was allowed; intranasal or oral corticosteroids were not permitted for the study duration. Written informed consent was obtained from each patient prior to enrollment.

The study investigators were asked to subcategorize each patient's sinusitis episode as either "acute sinusitis" or "acute exacerbation of chronic sinusitis." These subjective categorizations were used to compare clinical response with patient medical characteristics.

Study Design and Antimicrobial Therapy. This was a prospective, randomized, double-blind, multicenter comparative trial. The patients were randomly assigned to 1 of 2 treatment groups by means of a block design random code computer-generated at Bayer. The study drugs were encapsulated in #000 opaque gelatin capsules for blinding purposes. Ciprofloxacin (Cipro, Bayer Corporation, Pharmaceutical Division, West Haven, Conn) and CLARI (Biaxin, Abbott Laboratories, Abbott Park, Ill) were supplied as 250-mg tablets. All patients were to receive 2 capsules twice daily for 14 days. For patients randomized to CIP treatment, a matched placebo was taken from days 11 to 14. The patients were advised to take the study medication with the morning and evening meals and at least 120 mL of water.

Antimicrobial effectiveness was evaluated primarily by clinical response at the end of therapy (2 to 3 days posttreatment). Cultures were not obtained pretherapy, but sinus cultures were obtained by direct sinus aspiration (antral puncture or endoscope) in the case of clinical failure. Identification of causative aerobic organisms was performed by standard methods.[21] Susceptibility testing was conducted according to National Committee for Clinical Laboratory Standard (NCCLS) guidelines for minimum inhibitory concentration determinations.[22] All patients who received study medication made up the safety (intent-to-treat) population. The safety of drug treatment was assessed by clinical observations and by conventional laboratory tests of renal, hepatic, and hematologic function.

Efficacy Evaluation. For a course of therapy to be judged valid for drug efficacy, the following criteria must have been satisfied: 1) diagnosis of acute infection confirmed by clinical signs and symptoms and positive radiography consistent with acute maxillary sinusitis; 2) study drug given for 14 full days with 90% compliance, unless treatment was a failure; and 3) no other antimicrobial agent administered concomitantly with the study drug.

The effectiveness of the study drug was determined on the basis of the clinical response of the patient at the end of therapy and at the 28-day follow-up evaluation. Clinical response was based on serial examinations of the patient including improvement in sinus radiographs; disappearance or decrease in nasal congestion, postnasal drainage, or cough or throat clearing; disappearance or lessening severity of facial pain or headache; and reduction in white blood cell count and C-reactive protein (return to normal or >50% reduction from baseline). At completion of therapy (2 to 3 days posttherapy), the clinical response was defined as resolution (absence of all signs and symptoms related to the infection, and negative or improved radiography, such that additional antimicrobial therapy was not required); improvement (improvement of most signs and symptoms related to infection, and negative or improved radiography, such that additional antimicrobial therapy was not required); failure (no change, or worsening or reappearance of the signs and symptoms of infection, and no change or worsening of positive radiography, such that alternative antimicrobial therapy was required); or indeterminate (no evaluation possible). At the 28-day follow-up evaluation, clinical response was defined as resolution (clinically improved or resolved at the end of therapy and resolved at the 28-day follow-up); relapse (reappearance of any signs or symptoms related to acute sinus infection and positive radiography, thus requiring antimicrobial therapy); or indeterminate (no evaluation possible).

All patients who were considered treatment failures either during or at the end of study drug therapy were to receive appropriate treatment with an alternative antibiotic. These patients were then clinically evaluated 28 days following the date of their treatment failure and were assigned to the categories resolution (disappearance of signs and symptoms such that additional antimicrobial therapy was not needed); improvement (improvement of most signs and symptoms of infection with no additional antimicrobial therapy required); failure (no change, worsening, or reappearance of signs and symptoms present prior to alternative antimicrobial therapy); or indeterminate (no evaluation possible).

In addition to evaluation of the clinical response of all patients valid for efficacy analysis, an intent-to-treat analysis was also performed for all patients who received the study drug (safety population). All patients who were administered the study drug for any length of time were evaluated for drug safety (intent-to-treat population). Adverse events were rated by their severity (mild, moderate, severe, or serious or life-threatening) and by the relationship to the study drug (probable, possible, remote, or none).

Statistical Analysis. The goal of this study was to demonstrate that the CIP regimen was equivalent to that of CLARI. The primary measure of efficacy was the proportion of patients in each treatment group with clinical resolution or improvement at the end of therapy. With the sample size enrolled, the study had a power of more than 80% to detect equivalence between CIP and CLARI ($\alpha = 0.05$, 2-sided).

For the end-of-therapy and 28-day follow-up clinical responses, 2-sided 95% confidence intervals (CI95) were calculated for the differences between resolution (resolution plus improvement) rates; the Mantel-Haenszel weighting procedure was used to adjust for a possible center effect. The 2 treatments were considered equivalent at the 2.5% significance level if the lower confidence limit was at least −0.10. These analyses were performed for both the efficacy-valid and intent-to-treat populations.

To test the comparability of the study drug groups, categorical variables including demographic and medical characteristics were analyzed by a Cochran-Mantel-Haenszel test, adjusting for a possible center effect, or a χ^2 test, as appropriate. For continuous variables, an analysis of variance (ANOVA) model was fitted with treatment group, center, and

TABLE 1. DEMOGRAPHICS AND BASELINE MEDICAL CHARACTERISTICS OF EFFICACY-VALID POPULATION

Variable	*Ciprofloxacin (N = 236)*	*Clarithromycin (N = 221)*
Age, years		
Mean ± SD	40.4 ± 12.2	41.0 ± 13.1
Range	18-74	18-76
Sex, n (%) female	147 (62)	123 (56)
Race, n (%) white	227 (96)	207 (94)
Chronicity of infection, n (%)		
Acute	171 (72)	171 (77)
Acute exacerbation of chronic sinusitis	65 (28)	50 (23)
Location of current infection, n (%)		
Left sinus only	66 (28)	60 (27)
Right sinus only	65 (28)	77 (35)
Bilateral	105 (44)	84 (38)
Severity of current infection, n (%)		
Mild	13 (6)	16 (7)
Moderate	161 (68)	153 (69)
Severe	62 (26)	52 (24)
Duration of symptoms of current infection, days		
Mean ± SD	10.7 ± 6.5	10.2 ± 6.5
Range	2-30	1-29

None of differences between treatment groups were statistically significant.

treatment-by-center interaction as factors.

RESULTS

Study Population. Five hundred sixty patients with acute sinusitis were enrolled at 19 clinical sites. A total of 457 (82%) patients were valid for efficacy analysis (236 CIP, 221 CLARI); 559 patients were included in the intent-to-treat population. One patient was excluded from the safety analysis because no study drug was administered. One hundred three patients were not included in the efficacy analysis (46 CIP, 57 CLARI). The most common reasons for ineligibility included entry criteria violations (n = 37), nonadherence to study drug regimen (n = 29), and inadequate duration of treatment (n = 16). Of the 37 patients who did not meet entry criteria, 28 (11 CIP, 17 CLARI) patients had a nondiagnostic pretherapy sinus radiograph. The rates of, and reasons for, disqualification were similar between the 2 study drug groups. Forty-three patients were prematurely discontinued from the study drug (22 CIP, 21 CLARI). The most common reasons for discontinuation were adverse events (9 CIP, 9 CLARI), followed by patient noncompliance (6 CIP, 5 CLARI).

The baseline demographics and medical characteristics for efficacy-valid adults enrolled revealed no statistically significant differences between the 2 treatment groups with respect to age, sex, race, or health status (Table 1). The majority of the 457 efficacy-valid patients were females (approximately 60%), mean age was approximately 40 years, and 95% were white. With respect to chronicity, the preponderance of patients had an acute sinusitis episode (72% CIP, 77% CLARI) versus an acute exacerbation of chronic sinusitis. One hundred five patients (44%) in the CIP group and 84 (38%) in the CLARI group had a bilateral maxillary sinus infection. Overall, most patients had infections of moderate severity (68% CIP, 69% CLARI). The mean duration of symptoms for the current sinusitis episode was approximately 10.5 days for patients in both study drug groups. Allergic rhinitis was associated with the present sinus infection in 28% of CIP-treated and 24% of CLARI-treated patients. Approximately one third of patients reported at least 1 previous sinusitis episode in the 6 months prior to study enrollment. Fewer than 1% of patients in both treatment groups had sinus surgery within 6 months of study entry. Baseline demographic and medical characteristics in the intent-to-treat population were comparable to those for the efficacy population.

In the efficacy population, 14 (6%) CIP-treated and 17 (8%) CLARI-treated patients received an antimicrobial within 20 days of study drug onset. Cefuroxime axetil was the most common drug previously taken by patients randomized to CIP, compared to amoxicillin or tetracycline among CLARI recipients. During the trial, concomitant medications were administered to approximately 78% of patients in both treatment groups. For both study drug groups, concomitant agents predominantly included analgesics and cough and cold preparations. Nine patients in each group received concomitant antimicrobial agents, including 14 antifungal or antiviral agents. Of the 4 antibacterials given, 2 were topical agents, 1 was a urinary antiseptic, and 1 was a systemic antibacterial. Thirteen of the 18 patients received only topical antimicrobials, the majority to treat yeast infections.

Clinical Response. Clinical resolution or improvement at the end of therapy was reported in 84% of CIP-treated and 91% of CLARI-treated patients. At this specific end-of-treatment time point, CIP therapy was not statistically equivalent to CLARI therapy ($CI_{95} = -0.131, -0.0131$; Table 2). Further, since the upper bound of the CI was below 0, CLARI appeared to have a statistically significantly higher rate of success than CIP (p = .02). In contrast, the rate of clinical resolution at the 28-day follow-up, including end-of-therapy failures, was 79% of CIP patients, com-

TABLE 2. CLINICAL RESPONSE FOLLOWING CIPROFLOXACIN OR CLARITHROMYCIN THERAPY

		Ciprofloxacin		*Clarithromycin*		
Time of Evaluation	*Response*	*n/N*	*%*	*n/N*	*%*	*CI$_{95}$*
Efficacy-valid group						
End of therapy	Resolution	103/236	44	120/221	54	–0.131, –0.0131
	Improvement	96/236	40	82/221	37	
	Failure	37/236	16	19/221	9	
28-Day follow-up	Continued resolution	168/175	96	169/187	90	0.001, 0.108
	Relapse*	7/175	4	18/187	10	
Combined†	Resolution	168/212	79	169/206	82	–0.106, 0.044
	Failure	44/212	21	37/206	18	
Intent-to-treat group						
End of therapy	Resolution	119/272	44	139/267	52	–0.128, –0.017
	Improvement	108/272	40	103/267	39	
	Failure	45/272	16	25/267	9	
28-Day follow-up	Continued resolution	187/196	95	203/223	91	–0.006, 0.092
	Relapse*	9/196	5	20/223	9	

CI$_{95}$ — lower bound of 2-sided 95% confidence interval for difference in rate of resolution or improvement versus rate of failure.
*Excludes end-of-therapy failures.
†Combined end-of-therapy and 28-day follow-up analyses.

pared to 82% of those receiving CLARI, thereby demonstrating statistical equivalence between the 2 treatment regimens (CI$_{95}$ = –0.106, 0.044; Table 2); of note, an equivalence delta of –0.15 was used (Food and Drug Administration [FDA] definition) because the success rate for each group was below 90%. Notably, CLARI-treated patients had more than twice as many relapses as CIP recipients (18 versus 7, respectively; $p = .04$). Additional analysis revealed that if a patient was a clinical success at the end of therapy with a non-missing response at follow-up, the chance that the patient had a continued resolution at follow-up was 96% for CIP and 90% for CLARI (CI$_{95}$ = 0.001, 0.108). This latter analysis, which excluded end-of-therapy treatment failures, demonstrated the superiority of the CIP regimen. In summary, the overall outcome of the patients at the end of the trial (ie, combining clinical response at the end of therapy and at 28-day follow-up for all patients) indicated that the 2 drugs were equivalent in effectiveness. In general, results observed for the intent-to-treat population were similar to those for the efficacy-valid group (Table 2).

Causative Organisms in Treatment Failures and Relapses. Post-treatment cultures were obtained by sinus aspiration in 24 of 44 (55%) CIP failures and relapses and in 15 of 37 (41%) CLARI failures and relapses. Sixteen organisms were isolated from 13 CIP-treated patients, compared to 2 organisms isolated from 2 CLARI-treated patients; the remaining patients failed to have an organism identified at time of failure (14 CIP, 13 CLARI). Among the 18 isolated organisms, only 2 in each treatment group were among the 4 major sinusitis-causing pathogens: *H influenzae* (1 CLARI), *S pneumoniae* (1 CIP), *M catarrhalis* (1 CLARI), and *S aureus* (1 CIP). Of these 4 isolates, the *H influenzae* isolate was CLARI-resistant. The remaining 14 organisms isolated from CIP-treated patients included *Enterobacter aerogenes* (n = 1), *Pseudomonas aeruginosa* (n = 3), *Streptococcus* species (n = 7), *Pseudomonas fluorescens* (n = 1), and unspeciated gram-positive cocci (n = 2). Three of these 14 organisms (2 non-pneumococcal *Streptococcus* species and 1 unspeciated gram-positive coccus) were CIP-resistant. Of the 18 organisms isolated posttherapy, 15 were considered true pathogens (ie, colony counts >10,000 colony-forming units per milliliter); the 3 colonizing organisms were all isolated from CIP-treated patients, and all 3 were streptococcal species.

Potential Factors Related to Clinical Resolution. The relationship between clinical response and certain baseline medical characteristics was explored (Table 3). Age; gender; severity, chronicity, and location of sinus infection; and previous episodes of sinusitis in the last 6 months did not appear to significantly affect the clinical outcome of patients in either treatment group. In addition, logistic regression was performed of clinical response versus treatment group, severity of infection, chronicity, previous episodes, and location of infection. As shown above, treatment had a significant effect on clinical outcome at the end of treatment ($p = .035$). The effects of the other variables on clinical success failed to achieve statistical significance.

Medical characteristics and clinical response rates were compared between groups comprising 342 patients with acute sinusitis and 115 patients with acute

TABLE 3. CLINICAL RESOLUTION AT END OF THERAPY ACCORDING TO BASELINE CHARACTERISTICS IN EFFICACY-VALID POPULATION

	Ciprofloxacin		*Clarithromycin*	
Characteristic	*n/N*	*%*	*n/N*	*%*
Overall response	199/236	84	202/221	91
Severity				
Mild	12/13	92	15/16	94
Moderate	138/161	86	140/153	92
Severe	49/62	79	47/52	90
Chronicity				
Acute	148/171	87	158/171	92
AECS	51/65	78	44/50	88
Location of infection				
Unilateral	108/131	82	126/137	92
Bilateral	91/105	87	76/84	90
Number of previous episodes*				
No previous episode	139/160	87	153/166	92
At least 1 episode	58/74	78	49/55	89

AECS — acute exacerbation of chronic sinusitis.

*Within 6 months prior to study entry.

TABLE 4. MEDICAL CHARACTERISTICS AS FUNCTION OF CHRONICITY IN INTENT-TO-TREAT POPULATION

Medical Characteristics	*Acute Sinusitis*	*AECS*	*p*
Mean number of episodes in previous 6 months	0.29	0.73	<.01
Duration of present episode (days)	10.1	11.4	.045
Percent with at least 1 episode	22.2	48.3	<.01
Severity (%)			
Mild	7	6	NS
Moderate	69	70	NS
Severe	24	24	NS

AECS — acute exacerbation of chronic sinusitis, NS — not significant.

exacerbation of chronic sinusitis (Table 4). Although the mean number of previous episodes, duration of present episode, and percentage of patients with at least 1 previous episode were significantly different between the 2 comparison groups, clinical response was not found to be statistically significantly different (p = .16).

Safety and Adverse Events. Five hundred fifty-nine patients enrolled in this multicenter study were valid for safety. One hundred twenty (43%) CIP-treated and 158 (57%) CLARI-treated patients reported at least 1 treatment-emergent event. The majority of events were gastrointestinal–related (58 CIP, 81 CLARI), nervous system–related (19 CIP, 25 CLARI), or special senses–related (14 CIP, 60 CLARI). Specifically, 17 (6%) CIP-treated patients reported diarrhea, compared to 36 (13%) CLARI recipients. A notable finding was that only 7 (2%) of those receiving CIP experienced taste perversion, compared to 58 (21%) patients receiving CLARI.

Ninety-three (33%) CIP and 133 (48%) CLARI recipients experienced at least 1 possibly or probably drug-related adverse event. Diarrhea, nausea, headache, and dizziness were the most common events reported. Few adverse events were severe in intensity (12% CIP, 13% CLARI), and most improved or resolved spontaneously with sufficient follow-up. One episode each of arthralgia and tinnitus in the CIP group, and 1 episode each of peripheral edema, hyperuricemia, and pleural pain in the CLARI group were reported as unchanged at the final evaluation. Premature discontinuation of the study drug due to an adverse event was reported in 9 patients in each of the study drug groups; 3 of 9 CIP-treated patients required remedial drug therapies, compared to none in the CLARI group.

DISCUSSION

Acute sinusitis is a common infectious disease among adults, and associated with substantial morbidity. Additionally, the economic impact is considerable, particularly in lost workdays. This multicenter, double-blind study demonstrated that CIP was as clinically effective as CLARI when evaluating the combined clinical response rates (ie, combined end of therapy and 1-month follow-up) in the treatment of adults with acute maxillary sinusitis or acute exacerbations of chronic sinusitis as defined by FDA and Infectious Disease Society of America guidelines.[20] Importantly, the FDA currently considers response rates at 1 month posttherapy, rather than the end of therapy, to be a better predictor of an antimicrobial's efficacy.

The apparent inconsistency of the clinical response rate at the end of therapy and at the posttherapy follow-up between CIP and CLARI may be due to differences in length of active drug therapy and timing of the end-of-therapy evaluation. The CIP patients received active drug for 10 days (plus 4 days placebo), compared to 14 days among CLARI recipients. The end-of-therapy evaluation occurred similarly for both study drug groups (day 17). For CIP, however, this time point reflects a mean 7 days after the last day of active drug treatment. Many of the CIP treatment failures, therefore, may have been "early relapses" rather than true end-of-therapy failures. Despite the modest differences in clinical resolution between CIP and CLARI in this trial, clinical success rates with the fluoroquinolone were similar to those reported previously with CLARI in the treatment of acute sinusitis.[18,19]

At the 1-month posttherapy evaluation, patients were seen, on average, at day 43 for their final visit. At this final evaluation, CLARI was found to have more than twice as many clinical relapses (n = 18) as CIP (n = 7), a significant difference (p = .04). This finding was contradictory, as, theoretically, CLARI should have continued to be more effective than CIP. If the aforementioned "early relapses" for CIP had been included in the posttreatment follow-up evaluation, rather than at the end-of-therapy visit, the 2 study drug groups would not have been significantly different at this final evaluation and would have been equivalent at the end of therapy.

The bacteriologic cause of clinical failures and relapses (aerobes only) was also explored in this study. Approximately 40% to 50% of patients experiencing clinical failure or relapse had sinus cultures performed by aspiration. A finding of note was that about half of the CIP patients cultured had an organism isolated, although only 2 of 16 organisms (*S pneumoniae*, *S aureus*), both CIP-sensitive, were considered likely pathogens. In the CLARI group, only 2 organisms were identified (*H influenzae* [CLARI-resistant], *M catarrhalis*) among those who were clinical failures or relapses. The reason for clinical failure or relapse is unclear in many of the patients. Inappropriate specimen collection, low numbers of infecting organisms, bacterial suppression versus killing by antibiotic, and poor sinus drainage are several plausible explanations.

Clinical outcome was evaluated on the basis of baseline patient demographic and medical characteristics. Although clinical resolution at the end of therapy was not statistically significantly different within or between the treatment groups on the basis of age, gender, severity of infection, chronicity and location of sinus infection, or numbers of previous sinusitis episodes, several trends were observed. Patients with moderate and severe infections had a lower rate of clinical success regardless of the study drug used, whereas clinical success appeared equivalent between treatment groups for those patients with mild infections. Individuals with acute exacerbations of chronic sinusitis had a lower rate of clinical success in both treatment groups, compared to patients with acute sinusitis. In addition, patients who had no sinusitis episodes in the previous 6 months appeared to have a higher clinical success rate in both study drug groups. Further study of these variables may aid the clinician in identifying patients who may be more difficult to treat.

Several differences in specific adverse reaction rates were observed in this study. Gastrointestinal adverse events (mainly diarrhea) and taste perversion were reported more commonly in patients administered CLARI (13% and 21%, respectively) than in those given CIP (6% and 2%, respectively). Further, when we considered any adverse event in all body systems, CIP recipients had a lower rate of adverse events than CLARI-treated patients by 14%. These differences are of clinical significance in terms of patient safety and compliance.

In comparing double-blinded treatment trials, close attention needs to be paid to the definitions of outcome parameters as they relate to dose timing. The overall outcome of the patient at the end of the study is of paramount importance. Therefore, when combining clinical response at the end of therapy with clinical response at follow-up, the data imply that CIP and CLARI are therapeutically equivalent. While CLARI was statistically significantly more effective than CIP at the end of therapy (p = .02), CIP was statistically significantly more effective than CLARI at the 1-month follow-up (p = .04). These differences are not clinically significant, and when the end-of-treatment failures and the relapses at the 1-month follow-up were combined, CIP and CLARI were found to be equivalent ($CI_{95} = -0.106, 0.044$). This trial has demonstrated that CIP is effective and well-tolerated among adult patients with acute sinusitis or acute exacerbations of chronic sinusitis.

ACKNOWLEDGMENTS — We thank Adrienne L. Block, PhD, and Teresa Tartaglione, PharmD, for editorial and scientific contributions, and Amy Plofker for copy editing and preparation of the manuscript. The Sinusitis Infection Study Group was made up of the following individuals: Principal Investigator Alan Wanderer, MD, Clinical Research Center of Colorado, Englewood, Colo; Principal Investigator Leonard Y. Cosmo, MD, FCCP, Clinical Coordinator Kathleen J. Fischler, CRTT, CPFT, Tampa Medical Research Associates, Tampa, Fla; Principal Investigator Charles H. Banov, MD, Co-investigator Albert F. Finn, MD, Study Coordinator Robin Bostick, CRCC, Allergy & Asthma Centers of Charleston, Charleston, SC; Principal Investigator Gerald S. Gussack, MD, Co-investigator William J. Grist, MD, Study Coordinator Arlene Kehir, RN, Secretary Gwen McNeill, The Emory Clinic, Section of Otolaryngology, Atlanta, Ga; Principal Investigator Welby Winstead, MD, University of Louisville, Louisville, Ky; Principal Investigator Stanley P. Galant, MD, Co-investigators Chao-I Lin, MD, and William G. Harris, MD, Study Coordinator Joyce Williams, CMA-C, Clinical Trials of Orange County, Orange, Calif; Principal Investigator Donald Dvorin, MD, Study Coordinator Shelly Matez, RN, The Asthma Center, Mount Laurel, NJ; Principal Investigators Jon Aoki, MD, and John Herrod, MD, Clinical Coordinators Kayleen Whitelock, LPN, Laura Huck, David Huston, and Michael Thomas, Advanced Clinical Research, Salt Lake City, Utah; Clinical Coordinator Charlyn Marcusen, Advanced Clinical Research, Boise, Idaho.

REFERENCES

1. Vital and Health Statistics. National Ambulatory Medical Care Survey: US Department of Health and Human Services, Maryland, 1994. DHHS Publication No. (PHS) 94-1777.

2. Dingle JH, Badger GF, Jordan WS Jr. Illness in the home. A study of 25,000 illnesses in a group of Cleveland families. Cleveland, Ohio: The Press of Western Reserve University, 1964:347.

3. Schwartz R. The diagnosis and management of sinusi-

tis. Nurse Pract 1994;19:58-63.

4. Gwaltney JM. Acute community-acquired sinusitis. Clin Infect Dis 1996;23:1209-25.

5. Wald ER. Epidemiology, pathophysiology and etiology of sinusitis. Pediatr Infect Dis 1985;4:51-3.

6. Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A Jr. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90:457-62.

7. Brook I. Bacteriology of chronic maxillary sinusitis in adults. Ann Otol Rhinol Laryngol 1989;98:426-8.

8. Darouiche R, Perkins B, Musher D, Hamill R, Tsai S. Levels of rifampin and ciprofloxacin in nasal secretions: correlation with MIC90 and eradication of nasopharyngeal carriage of bacteria. J Infect Dis 1990;162:1124-7.

9. Falser N, Mittermayer H, Wade H. Antibacterial treatment of otitis and sinusitis with ciprofloxacin and penicillin V. A comparison. Infection 1988;16(suppl 1):S51-S54.

10. Saito H, Ohbori Y, Furuta S, Hashimoto M, Ohyama M. Laboratory and clinical studies on Bay o 9867 (ciprofloxacin) in otolaryngological field [in Japanese]. Chemotherapy 1985;33 (suppl 7):995-1009.

11. Mori Y, Baba S, Kinoshita H, Suzuki K, Shimada J. Laboratory and clinical studies on Bay o 9867 in otorhinolaryngological field [in Japanese]. Chemotherapy 1985;33(suppl 7): 978-87.

12. Fujimaki Y, Kawamura S, Watanabe H, Itabashi T, Nakamura M. Fundamental and clinical studies on Bay o 9867 (ciprofloxacin) in otorhinolaryngological field [in Japanese]. Chemotherapy 1985;33(suppl 7):970-7.

13. Baba S, Kinoshita H, Mori Y, Suzuki K, Shimada J. Clinical evaluation of ciprofloxacin in the treatment of paranasal sinusitis [in Japanese]. Otol Fukuoka (Jibi To Rinsho) 1987;33: 337-54.

14. Fombeur JP, Barrault S, Koubbi G, et al. Study of the efficacy and safety of ciprofloxacin in the treatment of chronic sinusitis. Chemotherapy 1994;40(suppl 1):24-8.

15. Legent F, Bordure P, Beauvillain C, Berche P. A double-blind comparison of ciprofloxacin and amoxycillin/clavulanic acid in the treatment of chronic sinusitis. Chemotherapy 1994;40(suppl 1):8-15.

16. Johnson PA, Rodriquez HP, Wazen JJ, et al. Ciprofloxacin versus cefuroxime axetil in the treatment of acute bacterial sinusitis. J Otolaryngol 1999 (in press).

17. Fraschini F, Scaglione F, Pintucci G, Maccarinelli G, Dugnani S, Demartini G. The diffusion of clarithromycin and roxithromycin into nasal mucosa, tonsils and lung in humans. J Antimicrob Chemother 1991;27(suppl A):61-6.

18. Marchi E. Comparative efficacy and tolerability of clarithromycin and amoxycillin in the treatment of out-patients with acute maxillary sinusitis. Curr Med Res Opin 1990;12: 19-24.

19. Karma P, Pukander J, Penttila M, et al. The comparative efficacy and safety of clarithromycin and amoxycillin in the treatment of out-patients with acute maxillary sinusitis. J Antimicrob Chemother 1991;27(suppl A):83-90.

20. Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS. Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Clin Infect Dis 1992;15 (suppl 1):S62-S88.

21. Murray PA, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of clinical microbiology. Washington, DC: American Society for Microbiology, 1995:6.

22. Approved Standard M7-A3. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 3rd ed. Villanova, Pa: National Committee for Clinical Laboratory Standards, 1993.

Ann Otol Rhinol Laryngol 108:1999

NASAL NITRIC OXIDE DOES NOT CONTROL BASAL NASAL PATENCY OR ACUTE CONGESTION FOLLOWING ALLERGEN CHALLENGE IN ALLERGIC RHINITIS

PHILIP E. SILKOFF, MBBS
DENVER, COLORADO

YEHUDA ROTH, MD
HOLON, ISRAEL

PATRICIA MCCLEAN, MSC
TORONTO, CANADA

PHILIP COLE, MD
TORONTO, CANADA

JERRY CHAPNIK, MD
TORONTO, CANADA

NOE ZAMEL, MD
TORONTO, CANADA

Nasal nitric oxide (NO), a powerful vasodilator, could control the filling of nasal capacitance vessels, thus determining nasal patency and mediating the acute congestion accompanying allergen challenge. We examined the effect of topical *N*-nitro-L-arginine-methyl-ester (L-NAME; 100 to 200 mg), an NO synthase inhibitor, on nasal NO and on nasal patency assessed by acoustic rhinometry in 7 subjects with nasal allergy, and in 4 subjects we examined the effects of nasal allergen challenge on nasal NO before and after a short course of nasal steroid. After L-NAME, nasal NO fell to 42.1% ± 15.7% of baseline ($p < .0001$) with no significant change in minimal cross-sectional area. After allergen challenge, acute congestion was associated with a significant fall in nasal NO, which returned to baseline by 4 hours, when the congestion resolved. Repeat challenge after 2 weeks of nasal corticosteroid yielded similar findings. A role for NO in modulating vascular tone was not supported by the present study.

KEY WORDS — acoustic rhinometry, L-NAME, nasal patency, nitric oxide, nose.

INTRODUCTION

The nasal cavities, nasopharynx, and paranasal sinuses excrete nitric oxide (NO),[1,2] a ubiquitous biological mediator subserving many diverse functions. In keeping with the known functions of NO as a vasodilator in the pulmonary and systemic vasculature,[3] NO could potentially cause vasorelaxation in the nasal vasculature. Inflammatory processes such as those occurring in allergic rhinitis have been associated with increased nasal NO concentrations,[4,5] which may be responsible for the hyperemia and hypersecretion[6] associated with inflammation. In addition, NO has an antimicrobial action[1] and may aid in maintaining sterility in the upper airway. There is also evidence that manipulation of NO synthesis can modulate ciliary motion.[7-9] The inhalation of NO from the nasal cavity is thought by some to modulate ventilation-perfusion relationships in the pulmonary circulation.[10]

Nitric oxide synthases (NOSs) of constitutive forms (cNOS), eg, endothelial or type III NOS (eNOS), and inducible forms (iNOS) exist in many cell types.[11,12] The latter is expressed in inflammatory diseases, and produces large amounts of NO compared with cNOS. In human sinus epithelium, iNOS may also be constitutively expressed.[1] In the rat nose, nerve fibers in blood vessels, glands, and epithelium are positive for NOS, and NO is a neurotransmitter.[13-15] In the human upper airway, eNOS is found in vascular endothelium, epithelium, and glands.[7] In chronic rhinitis and nasal polyp mucosa,[7,16] iNOS is expressed in respiratory and vascular epithelium, endothelium, smooth muscle cells, and inflammatory cells.

The paranasal sinuses in particular are a source of high NO concentrations relative to the lower respiratory tract.[1,2] This does not necessarily reflect increased production of NO in the sinus mucosa compared to other epithelia, as high concentrations may be due to decreased removal of NO, as the sinuses are poorly ventilated. In view of the unique nasal microvasculature and its role in the control of nasal airflow resistance,[17] we examined the effects of *N*-nitro-L-arginine-methyl-ester (L-NAME), an NOS inhibitor, on nasal patency, to indirectly determine the role NO plays in the control of blood content, and also to explore possible decongestant applications. We expected that the inhibition of nasal NO would be accompanied by an increased nasal patency due to decreased vascular filling in the nasal capacitance vessels. In addition, we postulated that if NO controls vascular congestion in the nose, then the acute congestive response associated with nasal allergen challenge should be accompanied by a rise in

---

From the Departments of Medicine (Silkoff, McClean, Zamel) and Otolaryngology (Roth, Cole, Chapnik), Faculty of Medicine, University of Toronto, Toronto, Canada. Dr Silkoff is currently at the Department of Medicine, National Jewish Medical and Research Center, Denver, Colorado. This study was supported by the Arnold and Leona Finkler Fellowship (P.S.) and by the Saul A. Silverman Family Foundation (Y.R.) and the Temmy Latner/Dynacare (Y.R.), a project of the Canada-International Scientific Exchange Program (CISEPO).

CORRESPONDENCE — Noe Zamel, MD, Mount Sinai Hospital, Room 656, 600 University Ave, Toronto, Ontario, Canada M5G 1X5.

nasal NO, and that on repeat challenge after a short course of nasal steroid, this rise might be attenuated.

We found that in subjects with nasal allergy, despite a significant fall in nasal NO concentrations following L-NAME administration, there were no salient changes in nasal minimal cross-sectional area (mCSA). Additionally, in 4 subjects, acute congestion on nasal allergen challenge was in fact associated with a significant fall in nasal NO, which returned to baseline by 4 hours, when the congestion had resolved. The same changes occurred on repeat challenge after a course of nasal steroid. A role for nasal NO in the control of the nasal microvasculature is not supported by the present study.

METHODS

A rapid-response analyzer (Sievers 270B, Boulder, Colo) with a response time of <200 milliseconds for 90% full scale was used for measurement of NO. This analyzer uses the principle of chemiluminescence, in which NO reacts with ozone to emit light that is detected by a photomultiplier tube. Calibrations to 2,000 parts per billion (ppb) were performed with serial dilutions of a standard NO gas (Praxair, Mississauga, Canada), and the analyzer sample flow rate was adjusted to 250 mL/min daily. The linearity of the analyzer response was verified by repeated calibrations.

Measurement of nasal NO was achieved with a "nasal cavity isolation technique" whereby NO excreted into the nose is sampled continuously. While seated, subjects performed quiet mouth breathing (room air) and were trained to close the velopharyngeal aperture. Anterior nasal closure was achieved by occluding both nares with soft silicone tubes. One tube sampled gas to the NO analyzer at 250 mL/min, while the contralateral tube allowed medical-grade air (21% oxygen, balance nitrogen; Praxair), which contains approximately 1 ppb NO, to be passively drawn from a reservoir into the other naris. The nasal cavities, nasopharynx, and sinuses thus acted as a communicating space "ventilated" by the intake of air generated by the suction of the analyzer. With the velum open, a real-time display of NO concentration showed low NO concentrations with tidal oscillations, while on velum closure, the NO concentration rose rapidly to reach a steady plateau within 30 to 40 seconds. This plateau concentration reflects air that has been conditioned with NO by passing through the nasal cavities. Velum closure was verified by carbon dioxide sampling from the nasal cavity that showed no carbon dioxide rise during the procedure. Three determinations of steady-state plateau NO that varied by <10% were made for each subject.

In extreme nasal congestion, eg, following allergen challenge, as the through-flow of air is impaired, the nasal isolation method is not suitable. In such an event, the seated subject breathed tidally through the nose into a small nasal mask and NO was monitored continuously from a port on the mask. The subject was encouraged to breathe at the normal rate and depth and recordings were made when the breathing pattern was regular and without apparent hyperventilation or hypoventilation. A small proportion of the NO measured with this method (3 to 5 ppb) originates in the lower respiratory tract.[18]

An Eccovision acoustic rhinometer (Hood Laboratories, Pembroke, Mass) was used. An adjustable support stabilized the cranium, the chin, and the rhinometer.[19] The Eccovision sound wave tube was applied by means of a plastic adapter to each nasal cavity in turn. The adapter tip was positioned to just contact the margin of the nostril, thus minimizing instrumental deformation of the compliant alar region, and the interface was sealed by generous application of a viscid water-soluble gel (Ecogel 400, Ecomed, Missisauga, Canada). Repeated measurements were obtained while nasal breathing was briefly suspended, until a total of 4 results showed mCSAs that varied by <5%. Total nasal mCSA was the sum of the left and right nasal cavities. Total nasal volume at 0 to 5 cm from the anterior nares was also assessed. A change of mCSA of >30% was taken a priori to represent a significant effect on nasal patency.

The study was approved by the Human Ethics Committee and performed in accordance with the 1983 Declaration of Helsinki. Twelve subjects (8 men and 4 women, age range 18 to 31) with a clear history of allergic rhinitis took part in the L-NAME and allergen studies. Subjects in the latter study had a positive skin test to grass or ragweed pollen at a concentration of <10 protein milligrams per milliliter. Exclusion criteria were within-previous-month use of nasal or systemic steroids, within-previous-month current upper respiratory tract infection, nasal polyps or significant septal deviation, smoking, oral antihistamines, moderate or severe asthma, and significant general medical conditions. All subjects completed a medical questionnaire and physical examination including anterior rhinoscopy.

N-nitro-L-arginine-methyl-ester (Sigma Chemicals, St Louis, Mo), an L-arginine analog and NOS inhibitor, was prepared in phosphate-buffered saline to a pH of 6.0 at a concentration of 50 mg/mL (manufacturer's limits of solubility). The L-NAME was given in repeated doses to a total dose of 100 to 200 mg by nasal atomizer spray (0.1 mL per activation)

NASAL PATENCY AND NASAL NITRIC OXIDE AFTER ALLERGEN CHALLENGE

	Nasal Nitric Oxide			*mCSA*			*Nasal Volume*		
Subject	*Baseline (ppb)*	*PC (% of Baseline)*	*LR (% of Baseline)*	*Baseline (cm^2)*	*PC (% of Baseline)*	*LR (% of Baseline)*	*Baseline (cm^3)*	*PC (% of Baseline)*	*LR (% of Baseline)*
First challenge (pre-steroid)									
1	660.0	49.0	91.0	1.71	71.9	77.2	19.9	48.1	51.8
2	856.0	55.0	77.0	1.58	54.4	55.1	12.5	69.7	72.6
3	840.0	38.0	83.0	1.65	41.8	97.0	11.9	64.1	147.0
4	851.0	45.0	108.0	1.13	78.8	118.6	10.2	91.9	113.8
Mean	801.8	46.8	89.8	1.52	61.7	87.0	13.6	68.4	96.3
SD	94.7	7.1	13.5	0.26	16.8	27.2	4.3	18.1	42.5
Second challenge (post-steroid)									
1	583.0	40.0	100.0	1.74	50.6	90.2	11.7	64.2	122.8
2	707.0	74.0	111.0	1.49	75.2	86.6	9.8	98.8	96.3
3	715.0	98.0	96.0	1.57	50.3	94.3	11.0	63.3	107.9
4	859.0	60.0	109.0	1.11	46.9	100.0	9.5	72.4	100.0
Mean	716.0	68.0	104.0	1.48	55.7	92.8	10.5	74.7	106.8
SD	112.9	24.5	7.2	0.27	13.1	5.6	1.0	16.6	11.7

mCSA — minimal cross-sectional area, PC — post-challenge, LR — late response (4 to 20 hours).

to achieve a fall in nasal NO (>30%). Subjects were instructed to tilt the head back and to avoid nose breathing for 1 minute following the drug administration. All subjects had monitoring of systemic blood pressure, pulse, and forced expiratory volume in 1 second (FEV$_1$) at frequent intervals throughout the study period.

Baseline acoustic rhinometry, nasal NO, FEV$_1$, blood pressure, and pulse rate were determined. L-NAME was administered to both nares at an initial dose of 50 to 100 mg, and nasal patency and nasal NO were measured repeatedly at 15- to 20-minute intervals. If nasal NO had not fallen at least 30%, further doses of L-NAME (50 to 100 mg) were given to a total dose of 200 mg (to avoid potential toxicity).

Baseline nasal NO and nasal patency were measured as described above. Subjects then had a nasal allergen challenge. Following the onset of acute congestion and additionally at the time of an expected late response (4 to 20 hours), nasal patency and nasal NO were reassessed. Following the initial challenge, subjects were started on beclomethasone dipropionate (Beconase, Glaxo), 100 μg twice per day to each naris for 2 weeks, and then a similar challenge and follow-up were performed.

Serial dilutions of grass and ragweed allergen (Dept of Allergy, McMaster University, Hamilton, Canada) were applied with a skin puncture technique with saline and histamine controls. Wheal size was assessed after 10 minutes.

Serial dilutions of grass or ragweed allergen (Dept of Allergy, McMaster University) were prepared in phosphate-buffered saline. The initial concentration for challenge was selected as 2 doubling concentrations below that causing a wheal 3 mm larger than the control. The allergen was administered from a nasal atomizer spray that delivered 2 activations of 0.1 mL to each nasal cavity. Doubling concentrations were then administered at 5-minute intervals until a change in nasal patency was observed.

The baseline values of nasal NO were compared with the minimal values by means of a paired 2-tailed *t*-test.

RESULTS

Following L-NAME administration, 1 subject felt transiently light-headed after the first dose, but this sensation was not associated with hemodynamic changes. Other reported symptoms included a salty taste and occasional transient mild stinging. No significant changes occurred in FEV$_1$, blood pressure, or pulse rate, monitored for 4 hours after the first dose of L-NAME. The baseline mCSA and nasal volume (mean ± SD) were 1.62 ± 0.34 cm^2 (range 0.98 to 2.0) and 12.47 ± 5.08 cm^3 (range 5.28 to 18.49). The baseline nasal NO was 652 ± 240 ppb (range 356 to 981). Nasal NO excretion was significantly reduced in all subjects by L-NAME administration to 42% ± 15.7% of baseline (range 23% to 60%, $p < .0001$). The time it took to reach nadir values was 71.4 ± 34.1 minutes. The mCSA, at the time of the maximal fall in nasal NO, was 88.3% ± 18.2% of baseline (range 65.2% to 123.4%; $p > .2$), and the nasal volume was 87.7% ± 21.7% (range 64.9% to 121.1%; $p = .18$), indicating a nonsignificant trend to nasal congestion.

One subject did not have a response to nasal allergen and was withdrawn. The results are presented in the Table. Allergen challenge produced sneezing and nasal congestion and/or rhinorrhea in all 4 subjects and caused acute congestion as assessed by acoustic rhinometry. In these subjects, there was an acute fall in nasal NO, which resolved by 4 to 20 hours, concurrent with a resolution of the nasal congestion. In 1 subject, it was necessary to employ the tidal breathing method of nasal NO measurement during the acute congestion. After treatment with nasal steroids for 2 weeks, the concentration of allergen required to cause an acute response was higher in 3 subjects, but there was no salient change in baseline or post-challenge nasal NO and nasal patency.

DISCUSSION

This study was performed to investigate the possible role of nasal NO in the modulation of nasal congestion. We found no change in baseline nasal patency after administration of L-NAME and a fall in nasal NO accompanying the acute congestion that occurred after allergen challenge in allergic rhinitis. These findings suggest that NO does not control resting vascular tone or mediate vascular congestion after allergen challenge.

Our results show that it is possible to partially inhibit nasal NO with the topical administration of L-NAME, but the effect varied considerably from subject to subject, with a maximum fall to 23% of baseline. This is in contrast to a previous study in which no fall in nasal NO occurred after topical administration of L-NAME[20] — possibly related to the dose, preparation, or administration of the compound. It is probable that the residual nasal NO after administration of L-NAME may be arising in the paranasal sinuses, which have high NO concentrations relative to the nasal cavity, and that topical L-NAME did not penetrate effectively to the less accessible sinuses. This residual NO may have continued to act on the nasal vasculature, masking the effect of L-NAME. Alternatively, a much higher dose of topical L-NAME or even systemic administration of L-NAME might allow the successful inhibition of sinus NO production.

Contrary to our hypothesis, L-NAME administration caused a nonsignificant trend toward nasal congestion. This indicates that nasal NO is not subserving a role in the control of basal capacitance vessel caliber. In agreement with our finding, but in nonallergic subjects, both Dear et al[21] and Rinder et al[20] reported a lack of effect of L-NAME on nasal cavity volume. However, in the latter study, nasal volume did correlate with nasal NO, and nasal decongestants reduced nasal NO. Similarly, Imada et al[22] reported that nasal NO seemed to be related to nasal resistance measured by rhinomanometry, as both measures fell after exercise as compared to baseline. However, this does not establish a simple cause-and-effect relationship.

In trying to understand the lack of effect of L-NAME on nasal patency, it is possible that the influence of other vasoactive control mechanisms such as the autonomic nervous system may be dominant over that of NO-mediated vasodilatation in the upper airway. Additionally, while the L-NAME solution was pH-corrected, the physicochemical attributes of the L-NAME preparation, eg, tonicity, may have had a congestant effect. Last, it may be that the effects of L-NAME would have been different if this group of subjects had been studied while symptomatic, when there was baseline nasal congestion, eg, in the acute allergy season.

Following nasal allergen challenge, we observed a fall in nasal NO with the onset of acute congestion, which returned to baseline once the acute congestion resolved. This response was the opposite of what would be expected if NO mediated the acute response. The same findings were found after repeat challenge following a 2-week course of nasal beclomethasone dipropionate. A similar fall in nasal NO after allergen challenge was reported by Kharitonov et al.[23] This fall in nasal NO postchallenge may be due to acute congestion and obstruction of the sinus ostia, as the paranasal sinuses contribute the bulk of the nasal NO concentration. Alternatively, the nasal hyperemia associated with the congestive response may cause increased absorption of NO, as hemoglobin is a powerful ligand of NO. As in the L-NAME study, it may be that the congestion following allergen challenge specifically is mediated via other vasoactive substances. Supporting this conjecture, Dear et al[21] reported that L-NAME had no inhibitory effect on allergen-induced nasal congestion, but that the acute congestion following nasal administration of bradykinin was abolished by prior L-NAME administration, and that this effect suggested an NO-dependent mechanism. At the time of a possible late response, no congestion was observed in any of the subjects, and nasal NO did not rise compared to pre-challenge levels.

It is of interest that nasal NO was unchanged after use of nasal corticosteroid. This may be due to the bulk of nasal NO arising in the sinuses, and poor distribution of the nasal steroid to the sinuses. Our findings are in agreement with a report by Lundberg et al[24] suggesting that nasal sinus iNOS is steroid-resistant, and agree with the lack of change in nasal lavage NO metabolites after steroid therapy reported by Garrelds et al,[4] but are in contrast with a report of high NO levels in non–steroid-treated compared with steroid-treated rhinitis.[23] It is possible that 2 weeks of nasal steroid was not long enough to show an effect.

In contrast to nasal patency, nasal NO seems to be involved in the production of nasal secretions, as Dear et al[25] reported that L-NAME inhibited the extravasation of albumin in response to nasal histamine and bradykinin. Other possible roles of nasal NO are discussed in the Introduction.

In conclusion, a role for NO in vascular control mechanisms regulating baseline nasal patency in subjects with rhinitis, and the mediation of acute allergic congestion, was not supported by our findings. Other vasoactive control mechanisms may be dominant over NO.

ACKNOWLEDGMENTS — We express our appreciation for the technical support given by Henry Furlott, Shobha Chakravorty, and T. Yoon.

REFERENCES

1. Lundberg JO, Farkas-Szallasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. Nat Med 1995;1:370-3.
2. Lundberg JO, Rinder J, Weitzberg E, Lundberg JM, Alving K. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. Acta Physiol Scand 1994;152:431-2.
3. Zapol WM, Hurford WE. Inhaled nitric oxide in adult respiratory distress syndrome and other lung diseases. Adv Pharmacol 1994;31:513-30.
4. Garrelds IM, van Amsterdam JG, de Graaf-in't Veld C, Gerth van Wijk R, Zijlstra FJ. Nitric oxide metabolites in nasal lavage fluid of patients with house dust mite allergy. Thorax 1995;50:275-9.
5. Martin U, Bryden K, Devoy M, Howarth P. Increased levels of exhaled nitric oxide during nasal and oral breathing in subjects with seasonal rhinitis. J Allergy Clin Immunol 1996;97:768-72.
6. Kulkarni AP, Getchell TV, Getchell ML. Neuronal nitric oxide synthase is localized in extrinsic nerves regulating perireceptor processes in the chemosensory nasal mucosae of rats and humans. J Comp Neurol 1994;345:125-38.
7. Furukawa K, Harrison DG, Saleh D, Shennib H, Chagnon FP, Giaid A. Expression of nitric oxide synthase in the human nasal mucosa. Am J Respir Crit Care Med 1996;153:847-50.
8. Schlosser RJ, Czaja JM, Yang B, McCaffrey TV. Signal transduction mechanisms in substance P–mediated ciliostimulation. Otolaryngol Head Neck Surg 1995;113:582-8.
9. Rosbe KW, Mims JW, Prazma J, Petrusz P, Rose A, Drake AF. Immunohistochemical localization of nitric oxide synthase activity in upper respiratory epithelium. Laryngoscope 1996;106:1075-9.
10. Gerlach H, Rossaint R, Pappert D, Knorr M, Falke KJ. Autoinhalation of nitric oxide after endogenous synthesis in nasopharynx [see Comments]. Lancet 1994;343:518-9.
11. Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH. Nitric oxide and the lung (NHLBI Workshop Summary). Am Rev Respir Dis 1994;149:1375-80.
12. Jorens PG, Vermeire PA, Herman AG. L-arginine–dependent nitric oxide synthase: a new metabolic pathway in the lung and airways. Eur Respir J 1993;6:258-66.
13. Ceccatelli S, Lundberg JM, Zhang X, Aman K, Hokfelt T. Immunohistochemical demonstration of nitric oxide synthase in the peripheral autonomic nervous system. Brain Res 1994;656:381-95.
14. Hanazawa T, Konno A, Kaneko T, et al. Nitric oxide synthase–immunoreactive nerve fibers in the nasal mucosa of the rat. Brain Res 1994;657:7-13.
15. Hanazawa T, Motosugi H, Konno A, Kaneko T, Tanaka K, Chiba T. Distribution of NADPH-diaphorase positive nerve fibers in the rat nasal mucosa. Neurosci Lett 1993;159:71-4.
16. Ramis I, Lorente J, Rosello-Catafau J, Quesada P, Gelpi E, Bulbena O. Differential activity of nitric oxide synthase in human nasal mucosa and polyps. Eur Respir J 1996;9:202-6.
17. Cole P. The nose. In: Mathew OP, Sant'Ambrogio G, eds. The respiratory role of the upper airways. New York, NY: Marcel Dekker, 1988:391-408.
18. Silkoff PE, McClean PA, Slutsky AS, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. Am J Respir Crit Care Med 1997;155:260-7.
19. Roithmann R, Cole P, Chapnik J, Shpirer I, Hoffstein V, Zamel N. Acoustic rhinometry in the evaluation of nasal obstruction. Laryngoscope 1995;105:275-81.
20. Rinder J, Lundberg JON, Anggard A, Alving K, Lundberg JM. Effects of topical nasal decongestants, L-arginine and nitric oxide synthase inhibition on nasal cavity nitric oxide levels and nasal cavity volume in man. Am J Rhinol 1996;10:399-408.
21. Dear JW, Ghali S, Foreman JC. Attenuation of human nasal airway responses to bradykinin and histamine by inhibitors of nitric oxide synthase. Br J Pharmacol 1996;118:1177-82.
22. Imada M, Iwamoto J, Nonaka S, Kobayashi Y, Unno T. Measurement of nitric oxide in human nasal airway. Eur Respir J 1996;9:556-9.
23. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. J Allergy Clin Immunol 1997;99:58-64.
24. Lundberg JO, Weitzberg E, Rinder J, et al. Calcium-independent and steroid-resistant nitric oxide synthase activity in human paranasal sinus mucosa. Eur Respir J 1996;9:1344-7.
25. Dear JW, Scadding GK, Foreman JC. Reduction by NG-nitro-L-arginine methyl ester (L-NAME) of antigen-induced nasal airway plasma extravasation in human subjects in vivo. Br J Pharmacol 1995;116:1720-2.

Ann Otol Rhinol Laryngol 108:1999

ANATOMIC STUDY FOR POSTERIOR MEDIALIZATION THYROPLASTY

HISAYOSHI KOJIMA, MD
KAZUHIKO SHOJI, MD
SHIGERU HIRANO, MD
NOBUHIKO ISSHIKI, MD
KYOTO, JAPAN

To attain posterior medialization by thyroplasty type I, we simulated the surgery using 3 cadaveric larynges. Two approaches were applied to adduct the arytenoid cartilage: one involved compression of the vocal process, and the other, compression of the muscular process inward. The inner perichondrium was incised to reach the arytenoid cartilage from the framework. To compress the vocal process, a large silicone plug was required. In this method, there was some difficulty in compressing the vocal process precisely, and there was the risk of postoperative extrusion of the large plug. In contrast, the muscular process was more superficial relative to the framework, and it could be precisely compressed, resulting in sufficient posterior glottal closure. The silicone plug required for this procedure has a shallow depth that may provide the advantage of preventing postoperative extrusion. In conclusion, the compression of the muscular process is preferable for safely achieving posterior glottal closure.

KEY WORDS — muscular process, posterior medialization, thyroplasty, vocal process.

INTRODUCTION

Thyroplasty type I, first proposed by Isshiki et al[1] in 1974, allows medialization and some augmentation of the paralyzed vocal fold by pushing inward the cartilage and the underlying soft tissue through the window made on the thyroid cartilage. It seems that this type of surgery has been widely accepted as a treatment of choice for unilateral vocal fold paralysis with dysphonia.

However, a number of modifications of the original technique followed in attempts 1) to enhance medialization of the posterior glottis,[2-9] 2) to facilitate the procedure by using a template,[3,5] or 3) to stabilize the postoperative course to avoid absorption of the window cartilage.[3,5,6,10]

As a result, a larger prosthesis, whatever the material is, tends to be used by some surgeons, frequently after removal of the window cartilage, directly on the inner perichondrium. A large prosthesis displacing the vocal fold and arytenoid cartilage medially will inevitably press hard on the soft tissues underlying the inner perichondrium and may even break the mucosa and be exposed or extruded into the airway.[11-13]

These modifications all predispose to complications from the use of alloplastic materials. It is well recognized that the complications not only are due to the chemical components of the implanted material, but also are due to physical features such as excessive size and sharp edges, as well. Once the foreign body is exposed to the airway, the only solution is to remove the whole material. Therefore, it would not be easy to maintain the effect that had been achieved by the prosthesis.

If thyroplasty type I were capable of safely medializing the posterior portion of the vocal fold, it would replace arytenoid adduction, which, though quite effective in eliminating a large posterior glottal chink, is certainly a little more complicated in terms of surgical procedure. However, before proceeding in that direction, a thorough investigation into the topographic relationships of the larynx is necessary to prevent any complications incurred by the use of a large prosthesis that directly touches the soft tissue.

MATERIALS AND METHOD

Three fresh human cadaver larynges (2 males and 1 female) without any history of laryngeal disorders were used for dissection to reveal the surgical anatomy related to an original thyroplasty type I and its modifications. The topographic relationships were videotaped for later analysis and further examination by computed tomography (CT).

More specifically, the following questions were examined in an attempt to find clinical answers.

1. How far can we medialize the retained inner perichondrium after removal of the window cartilage in thyroplasty type I?

2. What kind of topographic changes of the lar-

From the Department of Hearing and Speech Science (Otolaryngology), Kyoto University, Kyoto, Japan. This study was supported by a grant for Research on Eye and Ear Sciences, Immunology, Allergy and Organ Transplantation from the Ministry of Health and Welfare, Japan.

CORRESPONDENCE — Hisayoshi Kojima, MD, Dept of Hearing and Speech Science, Kyoto University, Sakyo-ku, Kyoto 606, Kyoto, Japan.

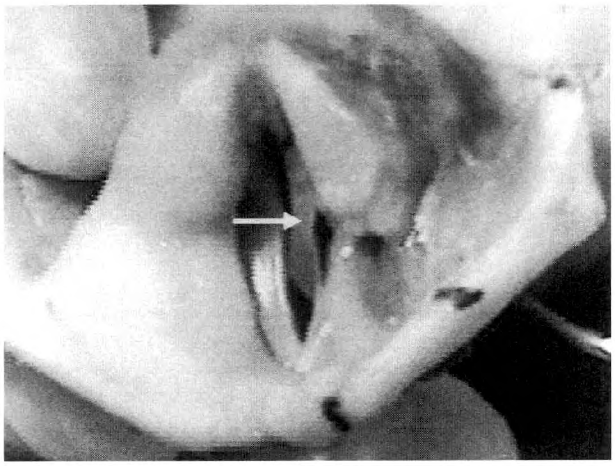


Fig 1. After separation of inner perichondrium from cartilage frame, perichondrium was pushed inward maximally. Depth was found to be about 7 mm, and vocal process (arrow) could not be compressed inward.

ynx occur when a large prosthesis is inserted through the window and the incised inner perichondrium all the way to the vocal process? And is it effective in medializing the posterior glottis?

3. How effective, safe, or easy is it to adduct or to medially shift the arytenoid and the posterior glottis by pressing the muscular process instead of the vocal process?

RESULTS

Maximal Medialization of Inner Perichondrium When Preserved Intact. A window was incised on the cartilage ala as described originally (5 × 10 mm), and the window cartilage was removed. After separation of the inner perichondrium from the cartilage frame by 2 to 3 mm in width, the perichondrium was pushed inward maximally. The depth was found to be about 7 mm (Fig 1). This figure naturally depends on how widely the separation is done around the window frame. Further medialization of the inner perichondrium is possible if the separation is extended far from the frame margin or the inner perichondrium is incised.

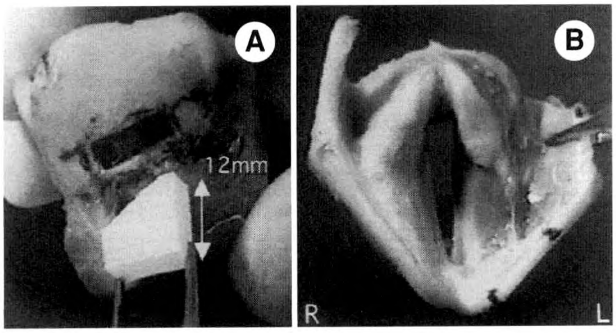


Fig 2. Procedure of compression toward vocal process. A) Silicone plug was designed with depth of posterior wedge 12 mm. B) Insertion of large silicone prosthesis toward vocal process brought about effective medialization of membranous vocal fold.

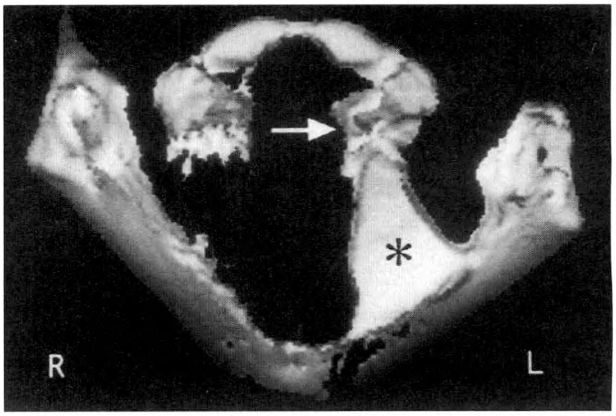


Fig 3. Three-dimensional computed tomography findings after compression toward vocal process (arrow). Effect of silicone plug (asterisk) on vocal process was slight.

Medialization by Pressing Vocal Process Inward. A medialization laryngoplasty as represented by the Montgomery procedure[3] was simulated on the excised larynx so as to have the large triangular implant with its posterior tip directly projecting to or on the vocal process. After cutting and removing the cartilage window, the inner perichondrium was incised to probe the vocal process and to insert the implant to the site most effective for the posterior medialization. The distance from the upper-posterior corner of the window to the vocal process was 12 mm in this case. Actually, it was not easy to identify, from this distance (the window), the vocal process, the base of which is surrounded by abundant muscle tissue. Insertion of the large silicone prosthesis toward the vocal process brought about effective medialization of the membranous vocal fold (Fig 2). However, CT revealed that the cartilaginous portion was hardly medialized, despite the large prosthesis (Fig 3).

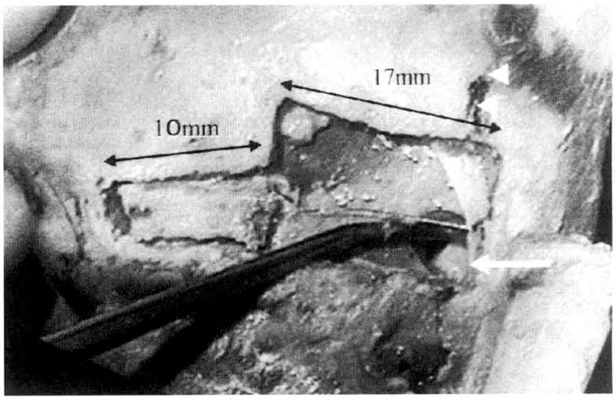


Fig 4. Location of muscular process. In this larynx, muscular process (white arrow) was located 17 mm posterior to posterior margin of original window and 5 mm deep to thyroid ala. White arrowheads — oblique line.

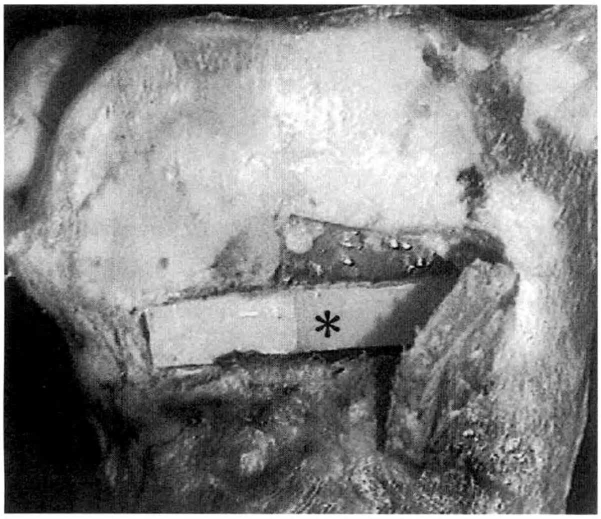


Fig 5. Long and thin silicone plug (asterisk) for compressing muscular process.

Medialization by Pressing Muscular Process Inward. An additional window was made posteriorly for easy access to the muscular process. Figure 4 shows the location of the muscular process. It was 17 mm posterior to the posterior margin of the original window and 5 mm deep to the thyroid ala. As the location of the muscular process depends on the size of the larynx, slight aberrations in these measurements may be unavoidable. Based on the above measures, an additional window, from which access to the muscular process is to be obtained, is designed at the oblique line of the thyroid cartilage. The prosthesis we designed had a long, thin posterior extension that projected toward the muscular process (Fig 5). Arytenoid medialization was achieved by insertion of the prosthesis (Fig 6). The CT findings showed effective medialization of the arytenoid cartilage by the silicone block (Fig 7). The pyriform sinus is located posterior to the muscular process. On the other hand, the laryngeal ventricle may easily be injured or violated during the undermining procedure because of its scarcity of soft tissue.

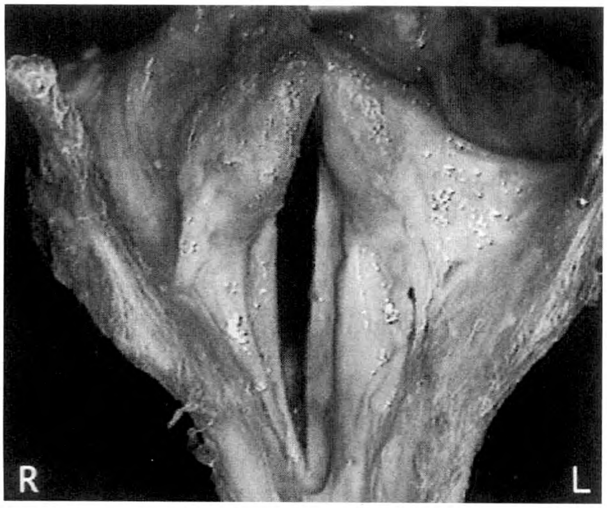


Fig 6. Laryngeal findings after compression of left muscular process. Good medialization of left arytenoid cartilage was obtained.

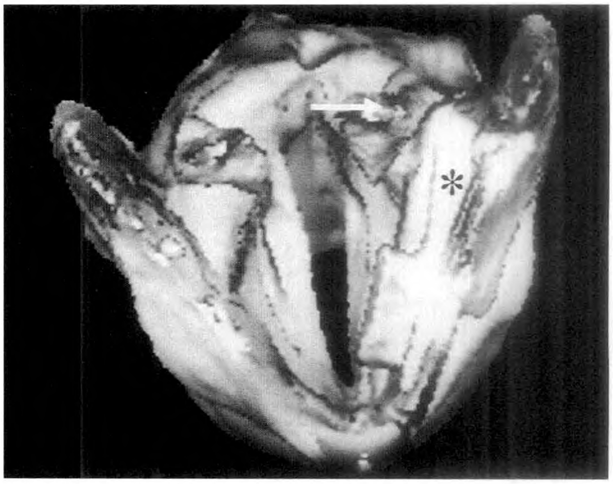


Fig 7. Three-dimensional computed tomography findings showed effective adduction of arytenoid cartilage by compressing muscular process (arrow). Asterisk — silicone plug.

DISCUSSION

In the original thyroplasty type I procedure, the cartilage window is made at the level of the vocal fold, with 5 to 7 mm from the median line of the thyroid cartilage left untouched. The size would be 4 to 6 mm in height and 10 to 12 mm in width. Although this is sufficient to medialize the membranous part of the vocal fold, the posterior glottal gap is left to be corrected by arytenoid adduction.

Recently, some modifications have been reported, mostly for the purpose of correcting the posterior glottal gap by using a modification of thyroplasty type I. The first problem is whether to preserve or incise the inner perichondrium. Some authors have attempted to correct the posterior glottal gap by keeping the inner perichondrium intact and using a silicone plug with a posterior wedge-shaped extension. However, our dissection experiment demonstrated that there was a limit in the extent of medialization of the posterior glottis, or else the arytenoid could not be shifted medially, unless the inner perichondrium was incised. Bielamowicz and Berke[7] reported that they could not correct a wide posterior glottal chink by thyroplasty type I preserving the inner perichondrium, even though the vocal process was medialized with a posteriorly extended silicone plug. In 1993, Montgomery et al[3] refined the prosthesis so that it projected toward the vocal process. In this method, the inner perichondrium was cut and a large silicone plug was inserted. They indicated that preservation of the inner perichondrium might result in undesired medialization of the paralyzed vocal cord. In our present examination, the arytenoid cartilage could not be moved medially unless the inner perichondrium was incised.

We conclude that for the purpose of medial shifting of the arytenoid cartilage in thyroplasty type I, the inner perichondrium needs to be cut either sharply under direct vision, or bluntly and gradually during the process of separation of the perichondrium from the cartilage.

In their thyroplasty, Montgomery et al[3] pressed directly against the vocal process. Our simulation of this procedure on the excised larynx indicated some difficulty in precise medial shifting of the vocal process, because it is located deep within a bundle of muscles. Tanaka et al[9] pointed out that while the vocal process is compressed directly inward with a large silicone implant, the muscular process may be pressed backward, resulting in insufficient posterior glottal closure. Moreover, the large silicone block required for enhanced medialization may be predisposed to postoperative extrusion. Tucker et al[11] reported 4 cases of extrusion of silicone implants, though they preserved the inner perichondrium after removal of the window cartilage. Cotter et al[12] had extrusion of the silicone in 8.6% of thyroplasty type I cases, which they ascribed to suboptimal placement. Generally, it can be said that a small silicone prosthesis would be preferable to a large one for the sake of preventing late extrusion and other complications.

Compared with the vocal process, the muscular process of the arytenoid cartilage is located more superficially, or closer to the framework, and can easily be identified following incision of the inner perichondrium. In the present study, when the lateral portion of the muscular process was compressed inward, the arytenoid cartilage slid medially, supplementing posterior glottal closure. Moreover, the risk of postoperative extrusion appears minimal, because the thickness of the silicone block required for this procedure is approximately 5 mm at the most. Thus, this muscular process compression technique seems preferable for arytenoid medialization, when performed as a part of thyroplasty type I.

Actually, one of the authors (N.I.) has successfully treated 2 cases of idiopathic displaced arytenoids with severe hoarseness by posteriorly enhanced thyroplasty type I, which shifted the arytenoid medially by blunt undermining from the routine window and by insertion of a long-tailed silicone prosthesis. The surgical outcome was reported as a part of the Paul Moore Lecture at the Joint Meeting of the Symposium on Care of the Professional Voice and the International Association of Phonosurgeons in 1996 in Philadelphia, Pa, and the details will be reported elsewhere.

The topographic relationship of the arytenoid to the thyroid ala naturally differs with the size of the larynx, particularly in male versus female larynges. Further, the rheological features are different between live and cadaver larynges. These experimental conditions restrict the quantitative implications of the results for surgery. However, the differences in the degree of medialization among different methods were so great that our conclusion seems warranted.

CONCLUSION

Within the framework of the present experimental conditions, it was indicated that medialization of the posterior portion of the vocal fold can be achieved more effectively, as well as more safely, by pressing the muscular process medially, rather than by pressing the vocal process.

REFERENCES

1. Isshiki N, Morita H, Okamura H, Hiramoto M. Thyroplasty as a new phonosurgical technique. Acta Otolaryngol (Stockh) 1974;78:451-7.

2. Isshiki N. Phonosurgery. Tokyo, Japan: Springer-Verlag, 1989:98.

3. Montgomery WW, Blaugrund SM, Varvares MA. Thyroplasty: a new approach. Ann Otol Rhinol Laryngol 1993; 102:571-9.

4. Desrosiers M, Ahmarani C, Bettez M. Precise vocal cord medialization using an adjustable laryngeal implant: a preliminary study. Otolaryngol Head Neck Surg 1993;109:1014-9.

5. Cummings CW, Purcell LL, Flint PW. Hydroxylapatite laryngeal implants for medialization. Preliminary report. Ann Otol Rhinol Laryngol 1993;102:843-51.

6. Netterville JL, Stone RE, Luken ES, Civantos FJ, Ossoff RH. Silastic medialization and arytenoid adduction: the Vanderbilt experience. A review of 116 phonosurgical procedures. Ann Otol Rhinol Laryngol 1993;102:413-24.

7. Bielamowicz S, Berke GS. An improved method of medialization laryngoplasty using a three-sided thyroplasty window. Laryngoscope 1995;105:537-9.

8. Ford CN, Unger JM, Zundel RS, Bless DM. Magnetic resonance imaging (MRI) assessment of vocal fold medialization surgery. Laryngoscope 1995;105:498-504.

9. Tanaka S, Tanabe M, Minoyama M, Iwanaga M. Thyroplasty for improvement of posterior glottis incompetence. J Jpn Bronchoesophagol Soc 1996;47:287-93.

10. Sasaki CT, Driscoll BP, Gracco C, Eisen R. The fate of medialized cartilage in thyroplasty type I. Arch Otolaryngol Head Neck Surg 1994;120:1398-9.

11. Tucker HM, Wanamaker J, Trott M, Hicks D. Complica-

tions of laryngeal framework surgery (phonosurgery). Laryngoscope 1993;103:525-8.

12. Cotter CS, Avidano MA, Crary MA, Cassisi NJ, Gorham MM. Laryngeal complications after type 1 thyroplasty. Otolaryngol Head Neck Surg 1995;113:671-3.

13. Rosen CA, Murry T, Woodson GE. Migration of the anterior segment following anterior commissure advancement: a case report. J Voice 1996;10:405-9.

≈

FIFTH INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Fifth International Conference on Head and Neck Cancer will be held July 29–August 2, 2000, in San Francisco, California. For information, contact Concepts in Meetings & Events, Robin L. Wagner, President, 7819 Lloyd Ave, Pittsburgh, PA 15218-1941; telephone (412) 243-5156; fax (412) 243-5160; e-mail rlwa@med.pitt.edu.

Ann Otol Rhinol Laryngol 108:1999

UTILITY OF RADIOGRAPHS IN THE EVALUATION OF PEDIATRIC UPPER AIRWAY OBSTRUCTION

DAVID L. WALNER, MD
CHICAGO, ILLINOIS
LANE F. DONNELLY, MD
DURHAM, NORTH CAROLINA
SERGE OUANOUNOU, MD
ATLANTA, GEORGIA
ROBIN T. COTTON, MD
CINCINNATI, OHIO

The evaluation of children with airway obstruction always involves a history and physical examination. The definitive diagnosis is most often made with microlaryngoscopy and bronchoscopy (MLB), and in cases of extrinsic compression, information is gained from magnetic resonance imaging. Although plain radiographs of the airway are often used as a primary diagnostic modality in children with airway obstruction, the accuracy of plain radiographs in predicting specific airway abnormalities has not previously been evaluated. This study was designed to correlate the findings of plain airway radiographs with the diagnosis made at the time of MLB. Medical records from 1991 to 1996 were reviewed to identify patients that had MLB and airway radiographs within 2 days of one another. One hundred forty-four cases were identified and divided into diagnostic categories. Statistical analysis showed a high sensitivity (>86%) for the accuracy of the radiologic diagnoses of exudative tracheitis, airway foreign body, and innominate artery compression. Laryngomalacia and tracheomalacia had a much lower sensitivity (5% and 62%, respectively). We believe that plain radiographic evaluation of the airway provides important information to the diagnostician. However, plain radiographs can be inaccurate and must be considered along with a history, physical examination, and clinical suspicion. Microlaryngoscopy and bronchoscopy remains the ultimate diagnostic test for airway disorders.

KEY WORDS — airway obstruction, radiographs.

INTRODUCTION

Pediatric upper airway obstruction is a condition that is cared for by primary care providers, pediatricians, emergency room physicians, and otolaryngologists. Because of the complexity of upper airway obstruction and potentially life-threatening situations that can arise, a prompt and accurate assessment of each patient is essential.

History and physical examination remain the hallmarks for assessment of these patients. Impending respiratory failure must be dealt with immediately by obtaining control of the airway. In the nonemergent situation, a thorough evaluation of the patient and any adjunctive studies that aid in making an accurate diagnosis are appropriate.

Plain radiographs of the airway have been utilized as the primary imaging modality in children with possible upper airway obstruction.[1,2] The radiographic studies are done to complement the clinical examination. Radiographs can be obtained quickly, and often provide diagnostic and anatomic details essential to preoperative planning. Information gained from airway radiographs about the subglottis and tracheobronchial tree is that which cannot be obtained by fiberoptic laryngoscopy in the awake child. For these reasons, radiographs of the neck in the lateral and anteroposterior planes are performed on almost all children being evaluated for stridor.[3] The use of radiographic studies in the evaluation of the child with stridor has been described as invaluable.[4] However, the accuracy of plain radiographs in predicting specific airway abnormalities identified on endoscopy has not been previously evaluated.

MATERIAL AND METHOD

A list of patients with a diagnosis of upper airway obstruction who underwent a microlaryngoscopy and bronchoscopy (MLB) between January 1991 and June 1996 was cross-referenced with a radiology database to identify patients who also had airway radiographs taken. All radiographs had been performed within 2 days of MLB. One hundred forty-four cases in 140 patients (ages 10 days to 19 years) were identified. Four of the patients had multiple MLB and radiographic studies. A staff pediatric radiologist (L.F.D.) who was unaware of the diagnosis made at the time of MLB retrospectively reviewed each of the radiographs.

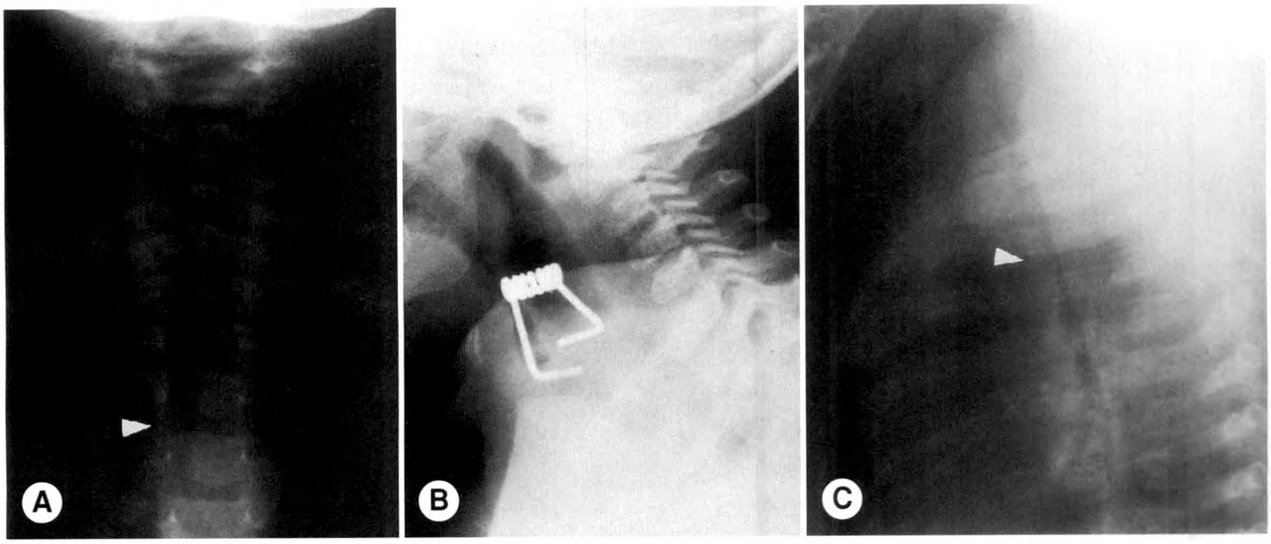
The MLB finding for each case was considered the definitive diagnosis. The radiographic findings

---

From the Departments of Pediatric Otolaryngology (Walner, Cotton) and Pediatric Radiology (Ouanounou, Donnelly), Children's Hospital Medical Center, Cincinnati, Ohio.

Presented at the meeting of the Society for Ear, Nose, and Throat Advances in Children, Cincinnati, Ohio, December 7, 1996.

CORRESPONDENCE — David L. Walner, MD, Dept of Otolaryngology/Bronchoesophagology, Rush-Presbyterian–St Luke's Medical Center, 1653 W Congress Pkwy, Chicago, IL 60612.



Radiographs of airway. A) Anteroposterior, showing irregularity along tracheal wall consistent with diagnosis of exudative tracheitis. Arrowhead — level of tracheal wall irregularity. B) Lateral, showing metallic foreign body in hypopharynx. C) Lateral, showing anterior compression of trachea at level of thoracic inlet (arrowhead). Consistent with innominate artery compression.

were evaluated for their correlation to the MLB findings and were classified as being precise, suggestive, not helpful, or misdiagnosed. Statistical analysis was performed for sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test.[5] All analysis was performed by grouping together radiographs that gave a precise diagnosis with those that were suggestive of the diagnosis, because these were both considered to be helpful to the clinician. Those radiographs that were not helpful or gave a misdiagnosis were grouped together, because they were both considered to be of no benefit to the clinician.

Radiographic Technique. Radiographs were performed in a recumbent position and taken during inspiration. For the anteroposterior film a 1-mm aluminum filter was used at a distance of 40 inches from the patient. The milliampere per second settings ranged from 0.25 in the infants up to 0.8 in the older children. The kilovolt potential settings ranged from 100 in the infants up to 115 in the older children. The lateral films were done without the use of a filter at a distance of 40 inches from the patient. The settings ranged from 2.5 to 3.2 mA/s, and the kilovolt potential was generally kept at 64.

Criteria Used to Make Radiographic Diagnoses. Exudative tracheitis (bacterial tracheitis, membranous croup) may show a linear airway filling defect; a tracheal wall plaque, membrane, or irregularity; or asymmetric subglottic narrowing. The narrowing can involve just the subglottis, just the trachea, or both (see Figure, A).

Foreign bodies of the aerodigestive tract are easily identified if they are radiopaque. Those that are radiolucent are often difficult to appreciate on plain radiographs. Radiolucent foreign bodies may show soft tissue density in or narrowing of the airway. Hypopharyngeal or esophageal foreign bodies can also cause airway compromise or posterior tracheal compression (see Figure, B).

Innominate artery compression is seen on lateral radiographs as anterior compression of the trachea at or just inferior to the thoracic inlet. The degree of compression ranges from near normal to severe (see Figure, C).

In croup (laryngotracheobronchitis), radiographs show symmetric subglottic narrowing or a "steeple sign." On the anteroposterior projection, edema of the subglottic mucosa symmetrically narrows the tracheal air column for about 5 to 10 mm or more below the level of the vocal cords. Ballooning and overdistention of the hypopharynx may be seen.[6] Subglottic or proximal tracheal stenosis can also have this appearance radiographically.

The films of patients with epiglottitis show enlargement of the epiglottis and aryepiglottic folds. Dilation of the pharyngeal airway can often be seen. Anteroposterior radiographs may only show a symmetric subglottic narrowing, similar to croup.

Patients with subglottic stenosis, scarring, or granulation tissue may have radiographs showing an abrupt and short segment airway caliber narrowing. If congenital subglottic stenosis is present, the cricoid cartilage often has an elliptical shape. This often appears radiographically as an hourglass constriction in the subglottic area.[7]

TABLE 1. ACCURACY OF RADIOGRAPHIC DIAGNOSES AS COMPARED TO MLB (N = 144)

	No.	*%*
Precise diagnosis	65	45
Suggestive of diagnosis	33	23
Not helpful	24	17
Misdiagnosis	22	15

Microlaryngoscopy and bronchoscopy (MLB) served as gold standard.

Subglottic hemangiomas often appear as an asymmetric subglottic narrowing or mass. Occasionally, the narrowing can appear symmetrically. Subglottic cysts can have the same radiographic appearance.

Congenital tracheal stenosis may appear on the plain radiograph as a missing segment. Intrinsic narrowing of the tracheal lumen may be seen with complete cartilaginous tracheal rings. Plain films of patients with tracheal stenosis may be normal or may underestimate the narrowing.[8]

Laryngomalacia is a dynamic process and therefore is not well seen on plain radiographs. If the film is taken during inspiration, inferior and medial bowing of the arytenoids, aryepiglottic folds, and epiglottis may be seen with ballooning of the laryngeal ventricle and hypopharynx.[9]

A diagnosis of tracheomalacia cannot be made on a single film. Due to the dynamic process of the condition, intermittent collapse of the airway can be seen when multiple films of the same view are taken or fluoroscopy is performed. Intermittent tracheal narrowing is seen at different times in the respiratory cycle. Tracheomalacia may be suspected if a single film shows diffuse long-segment tracheal narrowing.

RESULTS

After review of the MLB and radiologic diagnoses, the cases were classified into 8 different categories: normal, exudative tracheitis, laryngomalacia, subglottic stenosis, tracheomalacia, foreign body, innominate artery compression, and miscellaneous.

The radiologic diagnosis agreed precisely with the MLB diagnosis in 45% of the cases, was suggestive in 23%, was not helpful in 17%, and actually gave a misdiagnosis in 15% of the cases (Table 1).

TABLE 2. COMPARISON OF RADIOGRAPHIC AND MLB FINDINGS LISTED BY MLB DIAGNOSIS

	Radiographic Diagnosis			
MLB Diagnosis (No. of Cases = 144)	*Precise*	*Suggestive*	*Not Helpful*	*Misdiagnosis*
Normal (n = 33)	26	0	1	6
Exudative tracheitis (n = 32)	14	18	0	0
Laryngomalacia (n = 20)	0	1	13	6
Subglottic stenosis (n = 15)	6	6	1	2
Tracheomalacia (n = 8)	1	4	1	2
Foreign body (n = 8)	8	0	0	0
Larynx (n = 1)				
Trachea (n = 1)				
Esophagus (n = 4)				
Hypopharynx (n = 2)				
Innominate artery compression (n = 7)	6	0	1	0
Miscellaneous (n = 21)				
Croup (n = 2)	1	1	0	0
Subglottic hemangioma (n = 3)	1	0	0	2
Vocal cord paralysis (n = 2)	0	0	1	1
Laryngeal web (n = 1)	0	0	1	0
Subglottic papilloma (n = 2)	1	0	1	0
Bronchomalacia (n = 1)	0	0	0	1
Vocal cord edema (n = 1)	0	0	1	0
Redundant postcricoid mucosa (n = 1)	0	1	0	0
Tracheal edema (n = 1)	0	0	1	0
Lingual cyst (n = 1)	0	0	1	0
Vallecular cyst (n = 1)	1	0	0	0
Epiglottic mass (n = 1)	0	0	0	1
Tracheal stenosis (n = 1)	0	1	0	0
Laryngeal cleft (n = 1)	0	0	1	0
Laryngitis (n = 1)	0	1	0	0
Supraglottic mass (n = 1)	0	0	0	1

TABLE 3. SUMMARY OF MISDIAGNOSES

MLB Diagnosis	*Radiographic Diagnosis*
Normal (n = 6)	Bacterial tracheitis (2) Subglottic narrowing (2) Posterior subglottic mass (1) Tracheomalacia (1)
Laryngomalacia (n = 6)	Right arytenoid soft tissue mass (1) Symmetric subglottic narrowing (3) Tracheomalacia (2)
Tracheomalacia (n = 2)	Symmetric subglottic narrowing (2)
Subglottic hemangioma (n = 2)	Normal (1) Vascular ring (1)
Vocal cord paralysis (n = 1)	Possible tracheal web (1)
Bronchomalacia (n = 1)	Symmetric subglottic narrowing (1)
Subglottic stenosis (n = 1)	Tracheomalacia (1)
Epiglottic mass (n = 1)	Normal (1)
Supraglottic mass (n = 1)	Subglottic mass (1)

TABLE 4. STATISTICAL ANALYSIS OF RADIOGRAPHS

			Predictive Value	
Diagnosis	*Sensitivity*	*Specificity*	*Positive Test*	*Negative Test*
Exudative tracheitis	100%	97%	0.91	1.00
Foreign body	100%	100%	1.00	1.00
Innominate artery compression	86%	100%	1.00	0.99
Subglottic stenosis	80%	100%	1.00	0.98
Normal	79%	98%	0.93	0.77
Tracheomalacia	62%	97%	0.56	0.98
Laryngomalacia	5%	100%	1.00	0.87

A comparison of the radiologic diagnosis and the MLB diagnosis is presented in Table 2. A summary of the radiographs that actually provided a misdiagnosis is presented in Table 3. The most common misdiagnosis read on radiographs was symmetric subglottic narrowing or findings consistent with croup.

The results of analyses for sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test are presented in Table 4.

DISCUSSION

Importance of Airway Radiographs. Numerous authors suggest the use of plain radiographs in assessment of the airway. However, the accuracy of these radiographic assessments has not been addressed. Weber and Grillo[10] found conventional radiographs of the airway to be essential in the workup of benign and malignant tracheal lesions. In 1977, 31 children with stridor were reviewed, and the authors concluded by suggesting that in every case of congenital stridor a larynx radiograph (anterior and lateral) be performed.[11] Jasin and Osguthorpe[12] recommended plain radiographs of the airway in all elective evaluations of stridor.

Approach to Airway Radiographs. Radiographic evaluation of the upper airway must include both a frontal and a lateral view. Many conditions, such as exudative tracheitis or epiglottitis, may only be seen on 1 view, but cannot adequately be evaluated without both views. The films should be penetrated such that the entire airway from the nasopharynx to the carina is visualized on both views. Taking films during inspiration avoids pharyngeal tissue collapse and buckling of cartilaginous structures.[13] It is essential that the child's neck be in an extended position to avoid artifactual thickening of the retropharyngeal soft tissue. Tightly coned, high-kilovoltage, twice-magnified views of the airway should be obtained. The radiographic appearance of the pediatric airway is affected by positioning, crying, swallowing, and phase of respiration.[14] It is essential, when time allows, to obtain the best-quality radiographs possible and to repeat the films if need be. If a child has acute airway obstruction, he or she should not be placed in a supine position or immobilized, as these maneuvers might exacerbate the condition. These acutely ill children require prompt intervention.

In evaluating airway radiographs, airway abnormalities should be categorized as either extrinsic or intrinsic. These 2 subgroups not only lead us to consider different diagnoses, but also involve different workups and management plans. Suspected intrinsic causes of airway obstruction are evaluated and often treated with or at the time of endoscopy. Suspected extrinsic compression of the airway is evaluated with cross-sectional imaging, such as magnetic resonance imaging (MRI).

An anatomic approach to airway radiographs would include evaluation of the airway itself, as well as the adjacent soft tissue structures. Knowledge of normal radiographic anatomy is essential. The airway should be evaluated for focal narrowing or a change in caliber. When a focal narrowing is present, the description should include the location of narrowing from superior to inferior, the position of narrowing with respect to anterior and posterior (seen on lateral view), and, if narrowing is present, whether it is intrinsic or extrinsic. These factors help to focus the differential diagnosis.

The airway mucosa is normally smooth. Irregularity, indistinctness, and plaquelike deformities of the tracheal wall are abnormal. Compression of the distal trachea, carina, or main bronchi is often not visualized radiographically, and when compression of these regions is suspected, other imaging modalities such as MRI should be performed.[15] The soft tissues should be evaluated for focal enlargement. Areas often abnormal include the epiglottis, aryepiglottic folds, retropharyngeal soft tissues, and palatine and adenoid tonsils. Radiopaque foreign bodies, either in the airway or in the esophagus and compressing the airway, should be excluded.

Accuracy of Airway Radiographs. No data have previously been available to determine the accuracy of plain radiographs of the airway. The fact that the utility of radiographic studies has not been well addressed in the literature was emphasized in a recent paper on synchronous airway lesions.[16] In a comparison of tracheal dimensions measured by computed tomography scan and radiography in adults with goiter or tracheal tumor, only a moderate relationship of statistical significance was found.[17]

Mu et al[18] reviewed 343 cases of foreign body aspiration. They found radiography and/or fluoroscopy to accurately diagnose main stem bronchial foreign bodies in 65% of cases, segmental bronchial foreign bodies in 65%, tracheal foreign bodies in 22%, and laryngeal foreign bodies in 0%. Esclamado and Richardson[19] reviewed 13 patients with laryngotracheal foreign bodies. They found that the radiographs were suggestive of the foreign bodies in 12 of the cases.

With regard to imaging of laryngeal and tracheal stenosis, Hermans et al[20] stressed the use of computed tomography and MRI as providing the most information. They do comment that conventional radiography maintains its value in the initial evaluation of children with stridor, but the accuracy of this study is not specifically addressed.

Eliachar and Lewin[21] state that standard radiography serves as a primary screening study of the airway, but do not state its accuracy with regard to specific diagnosis or its overall use encompassing all diagnoses.

This study found a high sensitivity (100%) for diagnoses of exudative tracheitis and foreign body, and moderate sensitivity (79% to 86%) for the normal airway, innominate artery compression, and subglottic stenosis. Interestingly, the predictive value of a positive test was high (1.0) for diagnoses of foreign body, innominate artery compression, subglottic stenosis, and laryngomalacia. This information theoretically translates into believing a diagnosis that is made on radiography, but understanding that just because a radiograph does not describe a particular diagnosis suspected clinically, one cannot conclude that the entity does not exist. Tracheomalacia and laryngomalacia are unlikely to be diagnosed on plain radiographs, as we would suspect. Patients in our study who had a normal airway tended to have radiographic readings that overdiagnosed the actual condition. This was most likely related to selection bias, and the fact that all patients studied had known stridor that was significant enough to warrant an MLB. This was also identified by the low predictive value of a negative test in patients with a normal airway.

CONCLUSIONS

Although this is not a definitive study, what can be learned from this review is that history, physical examination, and clinical suspicion remain the hallmarks for predicting the presence of airway disease. Plain radiographs add some information and are often accurate in predicting what the actual disorder may be; however, they can be inaccurate or misleading, and a high index of suspicion must remain regardless of the radiographic diagnosis. Therapeutic designs should not be made on the basis of the radiographs alone. Endoscopy should be performed in patients with a clinical suspicion of airway obstruction, even in light of a normal radiograph.

REFERENCES

1. Holinger LD. Diagnostic endoscopy of the pediatric airway. Laryngoscope 1989;99:346-8.
2. Richardson MA, Cotton RT. Anatomic abnormalities of the pediatric airway. Pediatr Clin North Am 1984;31:821-34.
3. Tunkel DE, Zalzal GH. Stridor in infants and children. Clin Pediatr (Phila) 1992;31:48-55.
4. Handler S. Stridor. In: Fleisher GR, Ludwig S, eds. Textbook of pediatric emergency medicine. Baltimore, Md: Williams & Wilkins, 1993:474-9.
5. Campbell MJ, Machin D. Medical statistics. London, England: John Wiley and Sons, 1993.
6. Som PM, Curtin HD. Infectious and inflammatory conditions. In: Som PM, Curtin HD, eds. Head and neck imaging. St Louis, Mo: Mosby, 1996:585-90.
7. Silverman FN, Kuhn JP. Neck and upper airway. In: Silverman FN, Kuhn JP, eds. Caffey's pediatric x-ray diagnosis: an integrated imaging approach. St Louis, Mo: Mosby, 1993: 355-77.
8. Hedlund GL, Kirks DR. Respiratory system. In: Kirks DR, ed. Practical pediatric imaging: diagnostic radiology of infants and children. Boston, Mass: Little, Brown, 1991:515-707.
9. Smith RJH, Catlin FL. Congenital anomalies of the larynx. Am J Dis Child 1984;138:35-9.
10. Weber AL, Grillo H. Tracheal lesions. Assessment by conventional films, computerized tomography and magnetic resonance imaging. Isr J Med Sci 1992;28:233-40.
11. Kahn A, Baran D, Spehl M, Dab I, Blum D. Congenital stridor in infancy. Clin Pediatr (Phila) 1977;16:19-26.

12. Jasin ME, Osguthorpe JD. The radiographic evaluation of infants with stridor. Otolaryngol Head Neck Surg 1982;90:736-9.

13. Cotton RT, Reilly JS. Congenital malformations of the larynx. In: Bluestone CD, Stool SE, Kenna MA, eds. Pediatric otolaryngology. Philadelphia, Pa: WB Saunders, 1996:1299-306.

14. Macpherson RI, Leithiser RE. Upper airway obstruction in children: an update. Radiographics 1985;5:339-76.

15. Donnelly LF, Strife JL, Bisset GS. The spectrum of extrinsic lower airway compression in children: MR imaging. AJR Am J Roentgenol 1997;168:59-62.

16. Mancuso RF, Choi SS, Zalzal GH, Grundfast KM. Laryngomalacia. The search for the second lesion. Arch Otolaryngol Head Neck Surg 1996;122:302-6.

17. Demedis M, Melissant C, Buyse B, Verschakelen J, Feenstra L. Correlation between functional, radiological and anatomical abnormalities in upper airway obstruction (UAO) due to tracheal stenosis. Acta Otorhinolaryngol Belg 1995;49:331-9.

18. Mu L, Sun D, He P. Radiologic diagnosis of aspirated foreign bodies in children: review of 343 cases. J Laryngol Otol 1990;104:778-82.

19. Esclamado RM, Richardson MA. Laryngotracheal foreign bodies in children. Am J Dis Child 1987;141:259-62.

20. Hermans R, Verschakelen JA, Baert AL. Imaging of laryngeal and tracheal stenosis. Acta Otorhinolaryngol Belg 1995;49:323-9.

21. Eliachar I, Lewin JS. Imaging evaluation of laryngotracheal stenosis. J Otolaryngol 1993;22:265-77.

≈

EUROPEAN SOCIETY OF PEDIATRIC ORL

The Vth International Conference of the European Society of Pediatric ORL will be held July 9-13, 2000, in Graz, Austria. For more information, contact Claire Zwerina, Secretary to Prof Stammberger, ENT-Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43/316/385/3425.

Ann Otol Rhinol Laryngol 108:1999

PERCUTANEOUS TRACHEOSTOMY: A COMPREHENSIVE EVALUATION

KRIS S. MOE, MD
ZÜRICH, SWITZERLAND
SANDRO J. STOECKLI, MD
ZÜRICH, SWITZERLAND
STEPHAN SCHMID, MD
ZÜRICH, SWITZERLAND
ERNEST A. WEYMULLER, JR, MD
SEATTLE, WASHINGTON

Percutaneous tracheostomy (PT) is an ancient procedure that has recently attracted increasing interest. While there are numerous publications in the literature, there remains confusion due to the large variety of techniques and instruments with which it has been performed and the wide disparity in clinical outcome. This study evaluates the international literature on over 1,500 cases, classifies the techniques that have been used, analyzes the safety of each method, and reports a prospective outcome and cost analysis of 130 cases undergoing what we determined to be the safest method. We found that PT performed with the correct instruments and technique under bronchoscopic surveillance has a lower incidence of complications than open tracheostomy (OT). Cost estimation demonstrated that PT may be significantly more expensive than bedside OT. While we recommend PT as a relatively safe and expedient method of tracheostomy for selected intubated patients in an intensive care unit, it does not offer an advantage for patients who must be taken to the operating room, and should not deprive house officers of necessary experience in OT in this setting.

KEY WORDS — bronchoscopy, dilational tracheostomy, percutaneous tracheostomy.

INTRODUCTION

Tracheostomy is an ancient procedure, illustrated on Egyptian tablets as early as 3600 BC and described in the Talmud when the trachea of a goat threatened with suffocation was stented open with a reed pipe.[1] However, it has not always been widely accepted. Described by Caelius Aurelianus in the 5th century AD as a "senseless, frivolous, and even criminal invention of Asclepiades"; by Dante in the 7th century as "a suitable punishment for a sinner in the depths of the inferno"; and by D'Abano in the 13th century as "semi-slaughter," not until the 17th century was the procedure refined to the point that Fabricius could rejoice, "This operation redounds to the honor of the physician and places him on a footing with the gods."[1] The otolaryngologist Chevalier Jackson finally described in 1909 the method of tracheostomy currently used, and reported an unprecedented 3% mortality in 100 cases.[2]

Under pressures of economic efficiency and patient safety, there have been a growing number of publications on percutaneous tracheostomy (PT). As we have not found a formal definition of PT elsewhere, we shall refer to it as the insertion of a tracheostomy tube without direct visualization of the trachea, using minimal dissection, through the smallest incision possible. Percutaneous tracheostomy is also an ancient practice. In the 16th century, Santorio described the placement of a pointed tube through the skin into the trachea.[1] Mortality with this "stab" technique must have been quite high, and Jackson condemned its use: "...it is small wonder if the percentage of mortality is almost as high as of stab wounds, inflicted with homicidal intent."[2(p285)] But the need of methods for emergent and military use prompted continued research. Sheldon et al[3] reported in 1957 the use of a cutting instrument passed into the trachea along a guide needle, over which a tracheostomy tube was introduced. They stated that this required less than a minute and had minimal bleeding, no morbidity, and no mortality in 4 years' use. It was not stated how many procedures were performed, and there is little further mention of their technique in the literature.

In 1969, Toye and Weinstein[4] reported the first "dilational" technique of PT. This involved inserting a tracheostomy tube loaded over a curved dilator. They required only 30 seconds to perform the task, and in 1986 reported 94 cases, with no surgical mortality.[5] In 1985, Ciaglia et al[6] reported the use of a percutaneous nephrostomy set for tracheostomy, using the Seldinger technique[7] to pass dilators over a wire into the tracheal lumen. The initial 26 patients suffered no complications.

There are now publications on PT from more than 6 specialties internationally. Numerous instruments,

---

From the Department of Otolaryngology–Head and Neck Surgery, University Hospital of Zürich, Zürich, Switzerland (Moe, Stoeckli, Schmid), and the Department of Otolaryngology–Head and Neck Surgery, University of Washington, Seattle, Washington (Weymuller).

CORRESPONDENCE — Kris S. Moe, MD, Division of Otolaryngology–Head and Neck Surgery, University of California, San Diego, 200 W Arbor Dr, San Diego, CA 92103-8895.

TABLE 1. COMPLICATIONS OF TRACHEOSTOMY BY TYPE AND METHOD

	Method								
	1	*2*	*3*	*4*	*5*	*6*	*USZ*	*AVE*	*OT*
No. of procedures	94	150	428	228	79	7	130	1,116	
Total complications	15 (16)	28 (19)	35 (8)	7 (3)	13 (16)	5 (71)	9 (7)	112 (10)	6%-66%
Type of complication									
Death	1 (1)	1 (0.7)	1 (0.2)			1 (14)		4 (0.4)	0%-80%
Major hemorrhage		1 (0.7)	1 (0.2)	2 (0.8)	3 (4)			7 (0.6)	0%-36%
Pneumothorax	1 (1)	2 (1.3)			2 (3)	1 (14)	1 (0.7)	7 (0.6)	0.5%-4%
Paratracheal insertion	6 (6)					1 (14)	2 (2)	9 (0.8)	0.5%
Accidental decannulation	1 (1)	3 (2)	2 (0.5)					6 (0.5)	3%-4%
Tracheal perforation					1 (1)	1 (14)		2 (0.2)	
Tracheostomy tube occlusion			3 (0.7)					3 (0.3)	1%-11%
Inability to complete procedure		7 (4.7)	1 (0.2)			1 (14)	3 (2)	12 (1)	
Cardiac dysrhythmia		2 (1.3)	1 (0.2)					3 (0.3)	1%-4%
Wound infection	1 (1)		5 (1)		2 (3)		1 (0.7)	9 (0.8)	1%-36%
Tracheal stenosis			1 (0.2)		2 (3)			3 (0.3)	0.4%-60%
Damage of tracheal cartilage		3 (2)						3 (0.3)	
Tracheoesophageal fistula		1 (0.7)						1 (0.09)	0.5%-2%
Tracheomalacia		1 (0.7)						1 (0.09)	
Subcutaneous emphysema	4 (4)	3 (2)	3 (0.7)		2 (3)		1 (0.7)	13 (1.1)	1%-3%
Mild hemorrhage		2 (1.3)	13 (3)	5 (2)			2 (2)	22 (2)	
Hematoma	1 (1)							1 (0.09)	
Stomal granulation tissue		4 (2.7)	3 (0.7)					7 (0.6)	
Change of voice			3 (0.7)					3 (0.3)	
Poor cosmetic result		2 (1.3)			1 (1)			3 (0.3)	

See text for description of methods 1-6. Numbers in parentheses are percentages.

USZ — University of Zürich Hospital, ie, present series; AVE — average of series in methods 1-6 and USZ; OT — open tracheostomy, references 9-13.

methods, and refinements have been proposed, with outcomes ranging from disasters that would make even Dante weep, to triumphs that Fabricius would savor. The present study reviews the international literature on PT, with particular regard to its safety and indications, and reports our prospective study at the University of Zürich with 130 procedures.

MATERIALS AND METHODS

Prospective Study. A prospective study was begun in 1994, the first phase of which was a randomized comparison with open tracheostomy (OT) and has been reported elsewhere.[8] As this study demonstrated a much lower incidence of complications with PT, the OT arm of the study was ended and the PT arm was continued, allowing analysis of a larger series and prolonged patient follow-up. The PT was performed by residents as described earlier.[8] All details of the procedure were recorded, including indication, duration, and any complications that were incurred either perioperatively or postoperatively. Patients were followed regularly during the first 2 weeks after surgery, and a final postoperative follow-up was performed at the end of the study.

Literature Review. The international literature on PT was reviewed. The data were divided into 6 groups based on the method of PT and equipment used. Note was made of all types of complications reported, and a list of 20 categories was compiled (first column of Table 1). The larger series and those that warranted discussion were then evaluated with regard to these complications and tabulated (Table 1). A review of the literature on OT[9-13] provided a range for comparison. For details on the methods of tracheostomy used, please see the literature.

RESULTS

Prospective Study. The PT procedure was performed on 130 patients. The average age was 54 years (range 18 to 92), and 80 were male and 50 were female. The median follow-up was 20.5 months (range 3 to 1,391 days). The average time to completion of the procedure was 20 minutes (range 6 to 60). There was a total of 9 complications, for an overall complication rate of 7% (Table 2). One patient sustained a unilateral pneumothorax after emergency transtracheal jet ventilation, which was followed by cricothyrotomy and finally PT for airway stabilization. Although this complication was likely the result of the prior procedures, it is analyzed as a complication of PT in this series. Paratracheal placement of the tracheostomy tube occurred in 2 cases, 1 of which was not monitored by bronchoscopy. (It is our policy to observe the procedure by flexible bronchoscopy through the endotracheal tube.) These complications were discovered immediately and corrected. Three cases had to be converted to OT. This was due to bleeding in 1 instance and inability to penetrate an apparently calcified trachea in 2 cases. There was 1 minor wound infection, which was treated by local wound care. One case of subcutaneous emphysema was noted, which resolved spontaneously. There were 2 cases that demonstrated a minimal amount of postoperative bleeding, which halted without treatment. Follow-up of these patients demonstrated no delayed sequelae, particularly, no symptomatic tracheal stenosis or suboptimal cosmetic outcomes.

Literature Review. The 20 most common complications encountered in the PT literature are listed in Table 1, and an analysis of the complications of the major series using PT is presented. This Table presents the data by method of PT, including the number of procedures reported and the number and percent of each complication.

Method 1 is that of Toye and Weinstein,[5] described briefly above. They reported a 16% incidence of complications, 1 fatality occurring when an inappropriately short tracheostomy tube was used in an obese neck and an accidental decannulation ensued. One patient suffered bilateral pneumothorax, most likely due to antecedent trauma. More important, the rate of paratracheal (false) insertion was 6%. There are few reports by other investigators using this method for comparison.

Method 2, that of Schachner et al,[14,15] used the Rapitrac Kit (Surgitech Medical, Sydney, Australia), passing a flexible guide wire through a 12-gauge needle into the trachea, introducing a "percutaneous tracheostomy tool" over the guide wire, and spreading its jaws within the trachea, through which the cannula is passed. They reported a 9% rate of complication and no deaths in 80 procedures. The only major complication was 1 case of ventricular fibrillation, not likely due to the method of tracheostomy. Other investigators were less successful with this method, however. Ivatury et al[16] had complications in 31% of their procedures, including 5 failures. They also noted a fatality due to bronchospasm. The results of Fisher and Howard[17] were worse, with a 56% complication rate and failures in 22% of the attempts. Pelausa[18] found that the instrument was too short (leading to false cannulation) and functioned poorly. Hutchinson and Mitchell[19] reported 2 cases of bilateral pneumothorax from false cannulation, 1 being fatal.

Method 3 is that of Ciaglia et al,[6] using the Cook kit as first reported in 1985. There were no complications in their initial series of 26 cases, and there have been numerous subsequent reports. Cook and Callanan[20] reported a series of 21 cases with 2 minor hemorrhages and an accidental decannulation (which was easily corrected) for a 14% incidence of complications. Marelli et al[21] reported 61 procedures, with complications in 9.8%. All of these were minor, with the exception of a fatality due to a cardiac dysrhythmia. To improve safety, Marelli et al confirmed satisfactory placement of the dilators bronchoscopically, in a fashion similar to that reported elsewhere.[22,23] Winkler et al[23] performed PT with bronchoscopic guidance in 71 patients; in 13 cases (18%), the initial puncture was incorrect and revised before dilation was begun. Bodenham et al[24] reported 20 cases. Their complication rate of 10% included a case converted to OT because of bleeding. Six patients in this series were coagulopathic, but no difficulties due to bleeding were encountered in these cases. Hazard et al[25] performed PT with a similar kit on 12 coagulopathic patients: 10 were uncomplicated and 2 required a single-unit transfusion (but not surgical control). Moore et al[26] reported 27 cases without a major complication; Leinhardt et al[27] had only 3 minor hemorrhages in 20 cases. Gillen and Yaremchuk noted 2 minor hemorrhages in 11 procedures (unpublished observations, 1993). The final report on the Ciaglia method, in 1992,[28] was a study of 170 procedures. The total incidence of complications was 8.2%, all minor.

Shrager et al[29] published a series of over 400 cases by this method. While not all details required for inclusion in Table 1 were available, the 5 authors had a combined overall complication rate of "approximately 5%." There were no major hemorrhages or subcutaneous emphysema, and accidental decannulation occurred in less than 1% of cases. There was 1 death, in a patient with "severe adult respiratory distress syndrome."

Method 4 was described by Griggs et al[30] to avoid multiple dilations. After beginning with the method of Ciaglia et al,[6] a modified forceps is inserted over the wire into the trachea and spread. A tracheostomy tube is then placed over a dilator, which is passed over the wire into the trachea. The morbidity was 1% and 4% in the 2 series published by Griggs et al.[30,31] They concluded that their method increased the simplicity and safety of the procedure; however, there are no notable reports of its use in other hands.

In method 5, Hazard et al[25,32] also modified the Ciaglia et al[6] technique by eliminating the dilator guide and using only 3 straight, sharper dilators. The rate of complication varied from 11% to 25% in their 2 publications, including a pneumothorax in each series and a perforation of the posterior tracheal wall.

The final type of PT is method 6, reported by Wang et al[33] using a kit manufactured by Shiley Inc (Irvine, Calif). The method of Wang et al appears overtly similar to that of Ciaglia et al,[6] but there were a number of subtle differences that diminished the safety significantly. First, the skin was incised more caudally, where the trachea lies deeper, Second, the Shiley kit has a narrower guide wire, which can bend more easily and allow kinking (and paratracheal insertion). Third, the guide wire is inserted and manipulated through a bare needle, rather than a catheter, and a needle can damage the tracheal walls and allow passage through the posterior trachea. Fourth, no note is made of the use of a guiding catheter, an important implement for preventing kinking of the guide wire and subsequent false passage. Finally, the stoma was dilated to 34F rather than to a full 36F. Bronchoscopic surveillance was not performed.

In the series of Wang et al,[33] 1 patient developed a pneumothorax from paratracheal insertion of the apparatus; a second procedure was converted to OT when a calcified tracheal ring prevented passage of the larger dilators; in a third case, passage of the tracheostomy tube through the posterior wall of the trachea into the tracheoesophageal groove proved fatal. They halted their series after 7 cases due to the excessive morbidity and mortality. We have found no other report of experience with the Shiley kit.

DISCUSSION

Overall, fatalities due to PT itself are quite rare, and there were none in our series. Of the 1,116 cases analyzed from major studies in the literature (Table 1), there were 4 deaths, or a 0.4% mortality overall. The mortality in the individual series ranged from 0% to 14%. The large variation is due partly to sample size (the latter figure representing 1 death in a series of only 7 procedures) and partly to technique. A similar disparity is noted in the literature on OT, with mortality rates reported from 0% to 80% (Table 1). While an average mortality rate of 3% based on a review of the literature has been proposed as typical for OT,[34] lower rates than this can be achieved with PT when properly performed.

The 4 fatalities presented above were due to paratracheal insertion; placement of a short tracheostomy tube (2.75 in long) in a patient with an obese neck that allowed accidental decannulation; inability to maintain the elevated airway pressures required in a patient with adult respiratory distress syndrome when dilating the stoma; and cardiac dysrhythmia, probably not due to the particular method of PT.

Major hemorrhage (requiring blood transfusion or surgical intervention) occurred in none of our cases, and in 0% to 4% of procedures in Table 1 (0.6% overall), as compared to 0% to 36% of cases of OT (Table 1). Of the 18 procedures performed on coagulopathic patients by using the Cook kit,[24,25] only 2 (11%) resulted in a major hemorrhage. We believe the lower incidence of both intraoperative and postoperative hemorrhage with PT results from the dilators and firmly fitting tracheostomy tube that provide continuous tamponade during and after the procedure.

Pneumothorax occurred in 0% to 3% of cases (0.6% overall), with the exception of the single case in the Wang et al[33] series of 7 that yielded a 14% incidence. The literature on OT varies from 0.5% to 4% for this complication (Table 1). Clearly, the lower the neck is entered, the higher the risk of pneumothorax for either PT or OT. With normal palpable anatomy, PT directed through the first or second tracheal interspace should be relatively safe.

Paratracheal insertion of the tracheostomy tube occurred in 0% to 6% of cases, excluding those of Wang et al.[33] The 6 instances in method 1 underscore the danger of using their dilating trochar. Wang et al felt that paratracheal insertion in their series was due to kinking of the guide wire anterior to a calcified tracheal cartilage, which allowed the dilators to pass anterior to the trachea. This might have been prevented by the use of a stiffer guide wire, as is used in the Cook kit. Introduction of the dilator perpendicular to the trachea, followed by caudal angulation after penetration — rather than by initial caudal angulation, as they illustrate — may also prevent this problem. Due to concern about possible misplacement of the tracheostomy tube, we and others[9,21,22] perform fiberoptic bronchoscopy to confirm positioning. We consider this an important safety measure.

Accidental decannulation occurred in 0% to 2% of cases. With the exception of Toye and Weinstein's[5] fatality with the Rapitrac kit, immediate recannulation was easily and uneventfully achieved. Several authors noted that the combination of minimal tissue dissection and the snug fit of the tracheostomy tube obtained with PT eliminates the false passages that are common with the broader tissue dissection typical of OT. We have also found this to be true, and observed a mature-appearing, direct stoma when decannulation was necessary as early as 24 hours after placement. This may confer a significant safety advantage.

Procedure failure occurred in 1% of attempts overall, the failures requiring conversion to an open technique. The failure rate of Schachner et al[14,15] of 4.7%

was the highest, and was due to failure of the dilating instrument to reach the trachea in obese or edematous necks. The 3 failures in our series were due to 1 case of bleeding in which a resident was learning the technique and 2 cases in which the dilators could not be passed between apparently calcified tracheal cartilages. These were easily converted to OT without complication. Thus, as failures may occur, the physician performing the procedure must be able to perform OT with facility, and the necessary instruments should be at the bedside.

Cardiac dysrhythmia was an uncommon complication in these series, with an average incidence of 0.3%, and there is no indication of excess morbidity or mortality from this source. Indeed, in those cases of PT in which it occurred, there was no indication that it was due to the procedure itself. More likely, these complications were the result of the anesthetic, or an underlying physical condition, assuming hypoxemia was avoided. The incidence of 0% to 1.3% in these series is slightly less than the 1% to 4% incidence quoted in several series of OT (Table 1).

Wound infection was reported in 0% to 3% of cases with PT (0.8% overall), and we had none requiring systemic antibiotic therapy. Statistics from 1% to 36% are published for OT (Table 1). Empirically, the avoidance of broad dissection and tissue disruption would be expected to result in a lower rate of wound infection, and this has been confirmed in a prospective randomized trial.[8]

Tracheal stenosis as a complication of PT has been investigated quite thoroughly. Schachner et al[14] performed PT on 20 animals. After sacrifice 1 to 3 months later, the trachea had healed with a smooth, "curtain-like" appearance and no tracheal stenosis. They then performed autopsies on 20 patients who had undergone PT and found tracheal stenosis in none. They also found no radiographic evidence in 22 patients studied, and on tracheoscopy in 10 patients at 3, 6, and 12 months after PT found smooth healing of the tracheal opening and no stenosis.[15] Toye and Weinstein[4] performed 14 autopsies and found no tracheal abnormalities. Ciaglia et al[6] had 1 case of radiographic evidence of subglottic stenosis, which cleared spontaneously. In a subsequent follow-up of 52 patients from 4 months to 5 years after PT, Ciaglia and Graniero[28] found no cases of tracheal stenosis. Hazard et al[32] found that 2 cases in 11 procedures (and 5 of 8 cases of OT in the same study) had stenosis on plain tomography, but it is unclear whether they were in fact symptomatic. While Stoeckli et al[8] found irregularity of the cartilage on postmortem histologic evaluation, this did not correlate with clinical symptoms. As most patients with clinical tracheal stenosis become symptomatic 2 to 6 weeks after decannulation and occasionally up to 3 months later,[35] the follow-up times allowed in the above studies would have captured most delayed cases had they occurred.

Subcutaneous emphysema was noted in up to 4% of procedures done by PT. In no cases was it by itself dangerous to the patient, except in the rare case when it indicated an underlying pneumothorax. The incidence in OT is similar.

Minor hemorrhage (requiring no transfusion or surgical intervention) was an insignificant problem with PT and occurred in up to 3% of patients, depending on the series. In our experience, and in the randomized trial of Stoeckli et al,[8] PT causes much less "oozing" both during and after completion.

As demonstrated, the safety of the numerous methods of PT as a combined group compares favorably with (and in most categories surpasses) that of OT. Several prospective studies have confirmed this. Leinhardt et al[27] reported a consecutive series comparing the Cook and Rapitrac systems with OT. They found the Cook kit to have the lowest complication rate, with fewer infections and better cosmesis than OT. Griggs et al[30] compared their method of PT with OT. They had complications in 3.9% of 153 percutaneous procedures (6 hemorrhages) versus 19% of open procedures (hemorrhage, tracheal obstruction, pneumothorax, wound infection, wound breakdown, and 1 fatality). The groups were not randomized, however, and may have been quite different in severity of illness and other parameters. In a randomized prospective trial, Hazard et al[32] performed 22 PTs and 24 OTs. They found a 58% incidence of complications and 1 fatality in the OT group, and complications in 25% of the PT procedures with no fatalities. They concluded that PT appeared to be superior to the conventional operation. Stoeckli et al[8] found an overall morbidity rate of 6% for PT, compared to 36% for OT ($p < .001$).

Not all methods of PT are equally safe. Those methods that rely on an instrument whose jaws are inserted into the trachea and spread have poor performance records. These include the Rapitrac of Schachner et al[14] and the guide wire dilator forceps of Griggs et al.[30] The insertion of a sharp instrument into the trachea without means of confirming its location, followed by blind spreading in what one hopes is the tracheal lumen, is dangerous. The fact that these techniques may be successful in the hands of the developer who uses it frequently is by no means assurance that others will duplicate the performance.

TABLE 2. CONTRAINDICATIONS TO PERCUTANEOUS TRACHEOSTOMY

- Anatomic
  - Pediatric or other small airway
  - Scarring in operative field
  - Obesity obscuring landmarks of palpation
  - Edema in pretracheal region
  - Mass or tumor in or near operative field
  - Patients difficult to intubate for any reason
- Pathophysiologic
  - Diseases of urgent or emergent nature
- Other
  - Nonintubated patient
  - Any case expected to be technically difficult

The use of sharp or rapidly tapered instruments is what has been traditionally referred to as the "stab" technique. The early method of Sheldon et al[3] is a classic example of this. Toye and Weinstein's[4] approach is another, in that while the instrument is inserted through the anterior tracheal wall through a needle, one has no knowledge of where the tip of this heavily tapered instrument actually lies. Moreover, the literature shows that an instrument does not have to be particularly sharp to perforate the intimately related structures that course through the neck and upper thorax.

The technique of Ciaglia et al[6] (method 3) avoids these pitfalls in several respects. A needle is placed into the trachea, and its position is confirmed by the aspiration of air. This needle is removed, leaving its softer cannula in place. From this point on, no sharp instruments are used, and inadvertent tracheal laceration or puncture is thereby avoided. Progressively larger blunt dilators are aligned on the guiding catheter, and the entire assembly is inserted forward as a unit, preserving assurance of intratracheal location. The gradual dilation maintains tissue pressure and hemostasis. Upon insertion, the tracheostomy tube continues to provide mild pressure and hemostasis, molding the tissues so that accidental decannulation may be easily remedied by reinserting the cannula through a single well-defined stoma.

As with any technique, there is the temptation to stray from the recommended method or skip steps in the interest of saving time. However, with the Cook kit there are no redundant procedures or unnecessary steps. The process is well outlined in both of the publications of Ciaglia et al,[6,28] in a video available from Cook Inc, and in the instructions provided with each kit. These resources should be studied carefully; other reports quoting the Ciaglia et al[6] technique may be erroneous. (For example, Wilson and Bodenham[36] describe an incision midway between the cricoid cartilage and sternal notch.) Deviation from the original method can be dangerous, and we believe the experience of Wang et al[33] with the Shiley kit may exemplify this. The Shiley kit is similar to the Cook kit, yet, as outlined above, it is not identical. Subtle differences in design may have produced dramatic differences in outcome. And while the candor with which Wang et al reported their series was necessary and laudable, we cannot agree with their generalized condemnation of PT.

Having analyzed the literature and our own experience, we believe that there are some definite contraindications to PT (Table 2). This procedure should not be performed on an awake patient or one whose airway has not been secured by an endotracheal tube. The pressure and traction placed on the trachea, as well as the stimulus of the guide wire in the airway, would be poorly tolerated with local anesthetic. While others have performed PT in urgent or emergent settings,[5,37] we believe there is no procedure faster, simpler, or more effective than cricothyrotomy. Anatomic contraindications include the pediatric or other airway that has not attained adult size, and patients with anatomy obscured by scarring, obesity, edema, or masses (eg, enlarged thyroid gland or tumor). Pathophysiologic contraindications include disease processes requiring urgent or emergent intervention, such as supraglottitis.

One of the apparent incentives to perform PT rather than OT is cost savings. While the calculation of these costs will vary with institutions, the same basic personnel and equipment are required for both bedside OT and PT (Table 3.) The main difference is that a disposable set of instruments and bronchoscopy are required for PT. Thus, the added cost to the hospital for PT as estimated in Zürich, Switzerland, is approximately $200 (not including maintenance and repair of the bronchoscope), and at our institution this results in an approximately 50% increase in the patient charge.

CONCLUSIONS

On the basis of our prospective study of 130 cases and review of over 1,500 published procedures using the various classifications of PT, we make the following conclusions.

1. The safest instrument set currently available is the Cook kit.
2. Proper use of the Cook kit with bronchoscopic surveillance, on adult patients who meet the criteria outlined above, has demonstrated a safety record that surpasses that of OT.
3. Percutaneous tracheostomy does not provide a cost savings in comparison to OT when compared

TABLE 3. COST COMPARISON OF PERCUTANEOUS VERSUS OPEN TRACHEOSTOMY

Cost-Incurring Item	*Required for Open*	*Required for Percutaneous*
Surgical team	Yes	Yes
Anesthesiologist	Yes	Yes
Nurse	Yes	Yes
"Open" instruments	Yes	Yes
"Percutaneous" instruments	No	Yes
Bronchoscope	No	Yes

in the same operating site (ie, at the bedside or in the operating room).

Concern has been raised that PT will deprive the house officer of important operating experience, a skill critical in managing the emergent airway. However, PT will not replace OT in the common situation in which tracheostomy is performed as part of a longer surgical procedure. In the latter instance, OT adds comparatively little time and is less expensive. Finally, as PT is not performed unless the patient is previously intubated, tracheostomy under local anesthetic and urgent tracheostomy (as well as pediatric tracheostomy) will continue to be performed by the open method.

According to our experience and evaluation of the literature, PT should be performed only by physicians with detailed knowledge of the anatomy and physiology of the upper airway, with skills in emergent tracheostomy, and preferably by surgeons with extensive experience in airway management and intubation. In addition, the supplies for conversion to emergent OT should be readily available at all times, regardless of the physician's degree of experience with the operation.

The theoretical safety of this procedure has been confirmed in the series discussed above, and demonstrated in prospective analyses. A new "gold standard" for tracheostomy has been set, and should serve as a comparison for new techniques to come.

ACKNOWLEDGMENT — The authors thank Emily R. Timmins, MA, for her invaluable support and assistance in the development of this project.

REFERENCES

1. Sercer A. Tracheostomy through two thousand years of history. Ciba Found Symp 1962;10:78-86.
2. Jackson C. Tracheostomy. Laryngoscope 1909;19:285-90.
3. Sheldon CH, Pudenz RH, Tichy FY. Percutaneous tracheostomy. JAMA 1957;165:2068-70.
4. Toye FJ, Weinstein JD. A percutaneous tracheostomy device. Surgery 1969;65:384-9.
5. Toye FJ, Weinstein JD. Clinical experience with percutaneous tracheostomy and cricothyroidotomy in 100 patients. J Trauma 1986;26:1034-40.
6. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilational tracheostomy. Chest 1985;87:715-9.
7. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol 1953;39:368.
8. Stoeckli SJ, Breitbach T, Schmid S. A clinical and histologic comparison of percutaneous dilational versus conventional surgical tracheostomy. Laryngoscope 1997;107:1643-6.
9. Stock MC, Woodward CG, Shapiro BA, Cane RD, Lewis V, Pecaro B. Perioperative complications of elective tracheostomy in critically ill patients. Crit Care Med 1986;14:861-3.
10. Schusterman M, Faires RA, Brown D, Flynn MB. Local complications and mortality of adult tracheostomy. J Ky Med Assoc 1983;81:885-8.
11. Head JM. Tracheostomy in the management of respiratory problems. N Engl J Med 1961;261:587-91.
12. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheostomy. Am J Med 1981;70:65-76.
13. Meade JW. Tracheostomy — its complications and their management. N Engl J Med 1961;265:519-23.
14. Schachner A, Yoel O, Sidi J, Rogev M, Heilbronn Y, Levy MJ. Percutaneous tracheostomy. A new method. Crit Care Med 1989;17:1052-6.
15. Schachner A, Ovil J, Sidi J, Avram A, Levy MJ. Rapid percutaneous tracheostomy. Chest 1990;98:1266-70.
16. Ivatury R, Siegel JH, Stahl WM, Simon R, Scorpio R, Gens DR. Percutaneous tracheostomy after trauma and critical illness. J Trauma 1992;32:133-40.
17. Fisher EW, Howard DJ. Percutaneous tracheostomy in a head and neck unit. J Laryngol Otol 1992;106:625-7.
18. Pelausa EO. Percutaneous tracheostomy: ready or not? J Otolaryngol 1991;20:88-92.
19. Hutchinson RC, Mitchell RD. Life-threatening complications from percutaneous dilational tracheostomy. Crit Care Med 1991;19:118-20.
20. Cook PD, Callanan VI. Percutaneous dilational tracheostomy technique and experience. Anaesth Intensive Care 1989; 17:456-7.
21. Marelli D, Paul A, Manolidis S, et al. Endoscopic guided percutaneous tracheostomy: early results of a consecutive trial. J Trauma 1990;30:433-5.
22. Paul A, Marelli D, Chiu RCJ, Vestweber KH, Mulder DS. Percutaneous endoscopic tracheostomy. Ann Thorac Surg 1989;47:314-5.
23. Winkler WB, Karnik R, Seelmann O, Havlicek J, Slany J. Bedside percutaneous dilational tracheostomy with endoscopic guidance: experience with 71 ICU patients. Intensive Care Med 1994;20:476-9.
24. Bodenham A, Diament R, Cohen A, Webster N. Percutaneous dilational tracheostomy. Anaesthesia 1991;46:570-2.
25. Hazard PB, Garrett HE, Adams JW, Robbins ET, Aguillard RN. Bedside percutaneous tracheostomy: experience with 55 elective procedures. Ann Thorac Surg 1988;46:63-7.

26. Moore FA, Haenel JB, Moore EE, Read RA. Percutaneous tracheostomy/gastrostomy in brain-injured patients. A minimally invasive alternative. J Trauma 1992;33:435-9.

27. Leinhardt DJ, Mughal M, Bowles B, et al. Appraisal of percutaneous tracheostomy. Br J Surg 1992;79:255-8.

28. Ciaglia P, Graniero K. Percutaneous dilational tracheostomy. Chest 1992;101:464-7.

29. Shrager JB, Sing RF, Anderson HL, Reilly PM, Schwab CW. Percutaneous endoscopic tracheostomy. Surg Rounds 1994;Dec:681-5.

30. Griggs WM, Worthley LIG, Gilligan JE, Thomas PD, Myburgh JA. A simple percutaneous tracheostomy technique. Surg Gynecol Obstet 1990;170:543-5.

31. Griggs WM, Myburgh JA, Worthley LIG. A prospective comparison of a percutaneous tracheostomy technique with standard surgical tracheostomy. Intensive Care Med 1991;17:261-3.

32. Hazard P, Jones C, Benitone J. Comparative clinical trial of standard operative tracheostomy with percutaneous tracheostomy. Crit Care Med 1991;19:1018-24.

33. Wang MB, Berke GS, Ward PH, Calcaterra TC, Watts D. Early experience with percutaneous tracheostomy. Laryngoscope 1992;102:157-62.

34. Pemberton LB. A comprehensive review of tracheostomy. Am Surg 1972;38:251-6.

35. Wood DE, Mathisen DJ. Late complications of tracheostomy. Clin Chest Med 1991;12:597-608.

36. Wilson RC, Bodenham ARI. Percutaneous tracheostomy. Br J Hosp Med 1993;49:123-6.

37. Griggs WM, Myburgh JA, Worthley LIG. Urgent airway access. An indication for percutaneous tracheostomy? Anaesth Intensive Care 1991;19:586-7.

* * *

MIDDLE EAR MECHANICS

The Second International Symposium on Middle Ear Mechanics in Research and Otosurgery will be held October 21-24, 1999, in Boston, Massachusetts. For information, contact Harvard MED-CME, PO Box 825, Boston, MA 02117; telephone (617) 432-1525; web site http://www.med.harvard.edu/conted/.

Ann Otol Rhinol Laryngol 108:1999

SCHNEIDERIAN PAPILLOMAS OF THE PHARYNX

R. LUCIAN SULICA, MD
WASHINGTON, DC
RICHARD F. DEBO, MD
UNIONTOWN, PENNSYLVANIA

BRUCE M. WENIG, MD
WASHINGTON, DC
ROY B. SESSIONS, MD
NEW YORK, NEW YORK

Sixteen cases of schneiderian-type mucosal papillomas arising in the nasopharynx and oropharynx are reported. The patients include 11 men and 5 women ranging in age from 45 to 79 years (median 62 years). In 12 patients, the papilloma was discovered as an incidental finding, and 2 patients complained of nasal airway obstruction. In the remaining 2 cases, information regarding the cause that led to discovery was unavailable. None of the patients had a prior or concurrent history of sinonasal (schneiderian) papillomas. Histologically, all of the tumors were identical to sinonasal inverted papillomas. Transnasal or transoral surgical excision was the treatment of choice. In 4 of the patients, recurrent tumor occurred within 6 months of initial resection, necessitating additional surgery. Extended follow-up information was available in 9 cases. Eight of the 9 patients are alive and have been free of disease over periods ranging from 15 to 201 months (median 114 months) from diagnosis. One patient was found to have a separate nasopharyngeal squamous cell carcinoma 14 months after the diagnosis of the schneiderian-type papilloma. This patient died secondary to the squamous cell carcinoma 30 months after his initial evaluation.

KEY WORDS — nasopharynx, schneiderian-type papilloma.

INTRODUCTION

Schneiderian papillomas are benign neoplasms that arise from the mucosa of the nasal cavity and paranasal sinuses. Papillomas may arise from any epithelial surface, but schneiderian papillomas are separate entities with a characteristic histologic appearance and a distinct clinical behavior. These lesions originate from the schneiderian membrane, which is the ectodermally derived mucosa that lines the nasal cavity and paranasal sinuses. The extent of this epithelium defines the area in which these papillomas are usually found.

Although schneiderian papillomas may grow into adjacent areas from an origin within the nasal cavity, their occurrence as a primary tumor outside the sinonasal area is extremely rare. Lesions in atypical locations may not be recognized, and appropriate treatment may not be given. Further, their behavior outside their normal territory has not been examined, and their potential to recur and to undergo malignant transformation remains unknown. This study was undertaken to better characterize these "ectopic" schneiderian papillomas.

MATERIALS AND METHODS

The data for this study were obtained by reviewing cases contributed to the Armed Forces Institute of Pathology in the 20 years from 1976 to 1996. This material originated from US military personnel and their dependents, as well as civilian subjects. Histologic material from each case was reviewed to confirm the original diagnosis. Follow-up information was solicited from contributing pathologists, surgeons, and the patients themselves or the next of kin of those deceased. The records of pathology departments and tumor boards at contributing hospitals were also sought. All cases in which the origin of the lesion was ambiguous were excluded. Cases in which there was a concurrent schneiderian papilloma in the nasal cavity were also excluded, even if the pharyngeal lesion appeared distinct. Cases with a history of schneiderian papilloma prior to the identification of the pharyngeal lesion were also discarded. Despite dedicated efforts, it was not possible to obtain complete information on all parameters in each case. In such instances, no information was assumed, and note of this is made in the review of clinical findings. Initially, 22 cases were identified in the Otolaryngic Tumor Registry of the Armed Forces Institute of Pathology, but after application of these criteria, 6 were eliminated from the study. These included 4 cases of concurrent sinonasal inverting papilloma and 2 cases of presumed recurrence of lesions initially identified in the nasal cavity. The remaining 16 cases are discussed below.

From the Department of Otolaryngology–Head and Neck Surgery, Georgetown University Medical Center (Sulica, Sessions), and the Department of Otolaryngic-Endocrine Pathology, The Armed Forces Institute of Pathology (Wenig), Washington, DC, and the Otolaryngology Service, Madigan Army Medical Center, Tacoma, Washington (Debo).

CORRESPONDENCE — R. Lucian Sulica, MD, Dept of Otolaryngology–Head and Neck Surgery, Georgetown University Medical Center, 3800 Reservoir Rd NW, Washington, DC 20007.

CLINICAL FEATURES OF SCHNEIDERIAN PAPILLOMAS OF PHARYNX

Case	*Age*	*Sex*	*Location*	*Clinical Information*	*Long-term Follow-up*
1	63	M	Nasopharynx NOS	Unknown symptoms	Not available
2	49	M	Nasopharynx, posterior midline	Asymptomatic; found during workup for SCCa of cervical node; patient received wide-field radiotherapy	Dead of SCCa of nasopharynx at 30 mo
3	63	M	Nasopharynx, right and midline	Asymptomatic; found during sinus surgery	Recurrence and reexcision at 50 mo; ANED at 201 mo
4	50	M	Nasopharynx NOS	Asymptomatic; found on gastrointestinal endoscopy for ulcer	ANED at 173 mo
5	67	M	Nasopharynx NOS	Pedunculated mass found after complaints of obstruction	ANED at 116 mo
6	52	F	Nasopharynx, right	Unknown symptoms	Not available
7	60	F	Oropharynx, left posterior	Asymptomatic; found on examination for chronic rhinosinusitis	Recurrence and reexcision at 6 mo; ANED at 115 mo
8	69	M	Nasopharynx NOS	Asymptomatic; found on workup for cervical node (benign)	Recurrence and reexcision at 2 mo; diagnosis made from second specimen; no further follow-up
9	56	F	Oropharynx, posterior	Asymptomatic; found on routine physical examination	Recurrence and reexcision at 3 mo; no further follow-up
10	71	M	Nasopharynx, posterior	Asymptomatic; found at endoscopy for SCCa in situ of vocal fold	ANED at 114 mo
11	79	M	Oropharynx, vallecula	Asymptomatic; found on routine examination	Not available
12	60	M	Nasopharynx, NOS	Obstructive mass	Not available
13	45	M	Oropharynx, low posterior	Asymptomatic; found on routine examination	Not available
14	75	F	Oropharynx, right posterolateral	Asymptomatic; found on routine examination; declined reexcision despite doubtful margins	ANED at 55 mo
15	71	F	Nasopharynx NOS	Asymptomatic; found on endoscopy for nasal polyposis	ANED at 15 mo
16	61	M	Nasopharynx, NOS	Asymptomatic; found during uvulopalatopharyngoplasty	ANED at 20 mo

NOS — not otherwise specified, SCCa — squamous cell carcinoma, ANED — alive with no evidence of disease (persistence or recurrence).

RESULTS

Clinical Features. The clinical findings of the study group are summarized in the Table. The mean age of the patients at the time of diagnosis was 62 (range 45 to 79). Eleven (69%) patients were male and 5 (31%) were female.

Most commonly, the tumors were discovered in otherwise asymptomatic patients. In the 14 cases in which it was possible to assess symptoms, only 2 patients (14%) complained of obstruction. The remaining 12 (86%) were asymptomatic. In this group, 4 lesions were incidentally discovered during office physical examination; all of these were oropharyngeal lesions. Three were identified during investigation of sinus-related complaints. Another 3 lesions were found during evaluation for suspected malignancy: 2 for evaluation of neck masses, 1 of which was known to represent squamous cell carcinoma, and the third on endoscopy done to evaluate a carcinoma of the true vocal fold. A single papilloma was identified during evaluation for obstructive sleep apnea. One lesion was noted on flexible esophagogastroduodenoscopy for reflux and ulcer disease.

Lesions occurred predominantly in the nasopharynx (11 of 16), but were also found in the oropharynx, including a single lesion of the vallecula (5 of 16). All lesions whose size was reported were less than 2 cm. Lesions were described as either polypoid or sessile, and were colored tan, gray, or white.

Histology. The histologic features in all of the tumors were essentially identical and demonstrated the typical features of sinonasal tract schneiderian papillomas. In all of the patients, the papillomas showed an inverted growth with downward extension of neoplastic proliferation from the surface epithelium (Fig 1). Direct transition from ciliated respiratory epithelium to the epithelial neoplastic proliferation was seen. The neoplastic epithelial proliferation was composed of multilayered epidermoid and/or ciliated columnar cells that showed cellular uniformity, cell maturation, and retention of cell polarity (Fig 2A). Mucocytes characterized by round cells with abun-

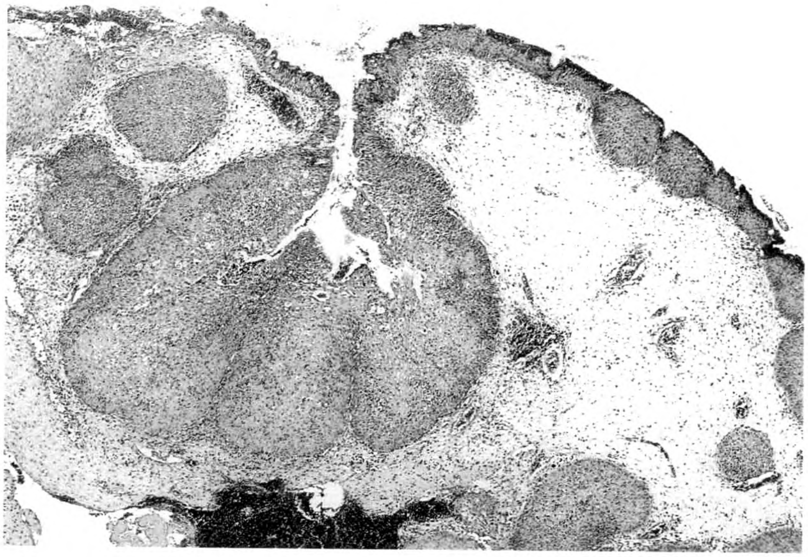


Fig 1. Nasopharyngeal endophytic or inverted schneiderian-type papilloma. Neoplastic proliferation takes origin from respiratory epithelium with bulbous extension into edematous and inflamed submucosa. Note separate rounded neoplastic nests within submucosa.

dant foamy to basophilic cytoplasm and an eccentrically located and compressed nucleus, and intraepithelial cystic spaces filled with inflammatory cells or mucinous material were seen within the surface epithelial component (Fig 2B). Mitotic figures were noted, but were limited to the area near the basement membrane. In a single case, focal surface keratinization was evident (Fig 3). Surface keratinization is an unusual feature for all types of schneiderian papillomas and has been thought to be a potential indicator of malignancy (synchronous or metachronous). However, neither this case nor any of the other cases showed cytologic features of a more aggressive epithelial proliferation (ie, dysplasia or overt malignancy). Additional features included an acute and chronic inflammatory cell infiltrate throughout the epithelial layer. The submucosal compartment showed a mixed chronic inflammatory cell infiltrate with associated edematous change. Submucosal cysts were not identified in any of the cases. The histology of the recurrent lesions in the group was identical to that of the primary neoplasm, that is, showing no evidence of dysplasia or malignancy.

Treatment and Follow-up. Reliable follow-up by a physician aware of the patient's diagnosis and history was available in 9 of 16 cases. The length of follow-up ranged from 15 to 201 months, with a median of 114 months.

There were 4 recurrences. Three lesions recurred within 6 months, a relatively short period of time, and were reexcised. The papilloma in the fourth of these patients recurred at 50 months. Following reexcision, this patient remained disease-free for an additional 150 months.

Initial removal was limited to local excision, either transnasal or transoral. Reexcision in all cases was also a limited procedure. No patient underwent excision via transfacial or transpalatal approaches.

Of note is a 49-year-old patient (case 2) whose papilloma was discovered during panendoscopy that was being done as part of the diagnostic workup of a neck node known to contain metastatic squamous cell carcinoma. An inverted-type papilloma of the nasopharynx was the only lesion found at the time of endoscopy. The tumor showed no evidence of malignancy, even upon retrospective review. The patient then received wide-field radiotherapy for an unknown primary. Fourteen months later, he received a diagnosis of squamous cell carcinoma of the nasopharynx. He went on to die of this cancer, 30 months from the original endoscopy, at the age of 51. This is the only case of this series to be associated with malignancy.

DISCUSSION

The sinonasal mucosa gives rise to a range of papillomas that Hyams[1] has grouped into 3 morphologic categories: inverted (endophytic), cylindrical, and exophytic. These benign neoplasms share certain tendencies: they recur if incompletely excised, they are able to invade surrounding tissues, and they possess a low but definite potential for transformation into squamous cell carcinoma. Allergy, polyposis, chronic infection, tobacco, and various occupational exposures have been proposed as etiologic factors.[1]

Several genotypes of human papillomavirus have been identified in sinonasal tract papillomas, and this virus may play an important role in the formation of the neoplasm.[2,3] The presence of human papillomavirus may be associated with tumor recurrence, and it has been suggested that certain subtypes (HPV16 and HPV18) convey greater malignant potential.[4,5]

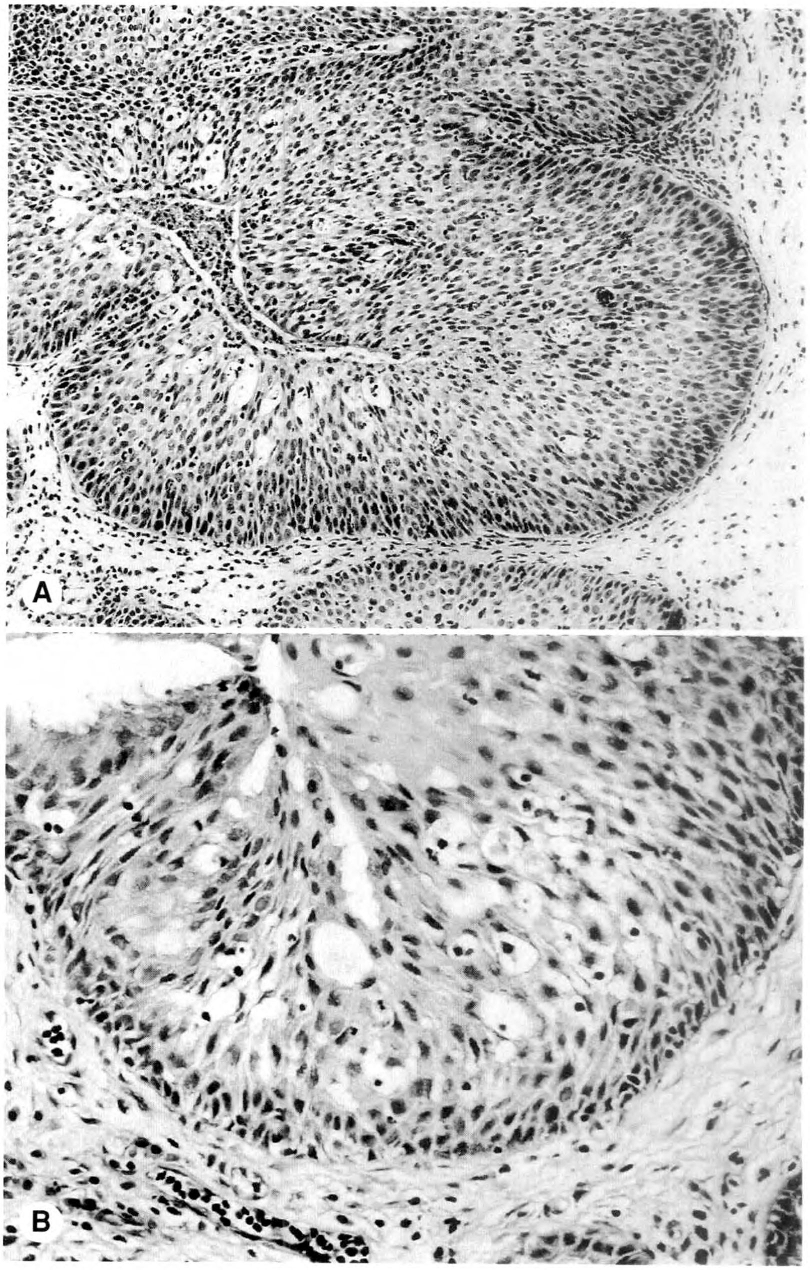


Fig 2. Nasopharyngeal inverted schneiderian-type papilloma. A) Epithelial component is multilayered, composed of benign epidermoid cells showing cellular uniformity, cell maturation, and retention of cell polarity. Cystic spaces filled with mucinous material and inflammatory cells scattered within epithelial tissue can be seen. B) Higher magnification shows presence of mucocytes.

Also, Epstein-Barr virus has been identified in association with sinonasal inverted papillomas.[6] In spite of these findings, an exact pathogenetic correlation remains obscure.

The ectopic occurrence of schneiderian papillomas — that is, outside the sinonasal tract — has been reported in 15 patients. Three of these cases occurred in the nasopharynx,[7-9] 2 in cervical lymph nodes,[10,11] 1 in the oropharynx,[12] 1 in the oral cavity,[13] 1 in the hypopharynx,[14] and 7 in the middle ear and mastoid.[15-18] Five of the lesions of the middle ear and mastoid originated from the Otolaryngic Tumor Registry of the Armed Forces Institute of Pathology.[18] In the 2 cases of inverted papilloma found in a cervical mass, both patients had a known lesion of the lacrimal sac. Neither the primary lesion nor the cervical one showed any histologic evidence of malignancy. While lesions of the lacrimal sac are unusual, they are not ectopic, as that structure has mucosa of the same ectodermal embryonic origin as that of the sinonasal tract. The cervical lesions were thought by the authors of those reports to represent lymphatic transport of benign neoplastic cells to lymph nodes.[10,11]

To explain these unusual lesions, a brief review of the embryology of the upper aerodigestive tract is helpful. At 3 to 4 weeks' gestation, bilateral thickenings destined to become the nasal placodes appear. Their central area becomes progressively more concave, with the resulting invaginations becoming

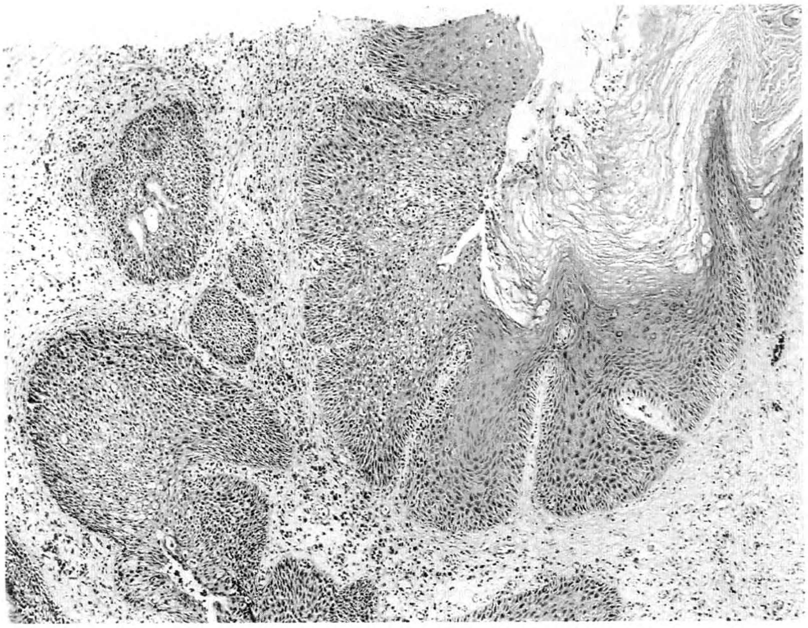


Fig 3. Nasopharyngeal inverted schneiderian-type papilloma. In 1 case, surface keratinization was found, but there was no cytologic atypia or histologic features of malignancy.

the nasal pits by week 5. The ectodermally derived epithelium that lines these ingrowths constitutes the schneiderian membrane. The fundus of these pits eventually comes into contact with the rostral end of the developing pharynx, lined by endodermal-derived epithelium of the branchial pouches. The bucconasal membrane, made of a layer each of ectodermal and endodermal epithelium, separates the 2 compartments. This structure breaks down, however, and thus allows free communication between the 2 cavities. By 10 weeks, the growth of the lateral palatal shelves separates the nasal compartment from the oral one, and the developing septum divides the nasal cavity into right and left halves. The choanae represent the watershed area between ectodermally and endodermally derived epithelia.[19] This process may occasionally result in the migration or incorporation of schneiderian mucosa into areas in which it is not normally found. Subsequent inflammation of this tissue, whether by environmental, viral, or other agents, may result in the development of the papilloma. It has been suggested that ectopic schneiderian papillomas represent migration of a previous sinonasal lesion.[16] However, in the absence of a previous lesion (grounds for exclusion in our series), we feel that embryological inclusion of normal schneiderian mucosa outside its normal range represents a more plausible explanation.

Our review shows that the clinical and pathologic features, as well as the biologic behavior, of pharyngeal schneiderian papillomas are similar to those of their intranasal counterparts. The demographic features of our cases are similar to those reported in several large series of intranasal schneiderian papillomas,[1,20-22] including a greater tendency to affect older men. Although lesions in our series appear to be unusually small and limited in extent, both of these observations may be artifacts of case selection. Because the precise origin of larger tumors is frequently difficult to assess, these tended to be excluded from the series. Thus, we feel the potential for growth and local extension of ectopic schneiderian papillomas is understated by our data.

Nasopharyngeal and oropharyngeal schneiderian papillomas, like the sinonasal lesions, have an increased potential for local recurrence if incompletely excised. Our rate of recurrence (44%), higher than those in several other surgical series,[20-22] probably reflects a high rate of incomplete initial removal, resulting from the unexpected nature of the lesion. Indeed, 3 of the 4 recurrent lesions in this report reappeared within 6 months.

We do not think that the single case of apparent malignant transformation was precipitated by radiotherapy, as malignant tissue was present in a neck node on the patient's initial presentation. Material from the excision was reviewed for this paper, and no signs of malignancy appear to have been overlooked. Thus, while this case does not indisputably demonstrate carcinoma ex papilloma, it certainly presents a compelling argument that ectopic papillomas share the malignant potential of the lesions found in the more usual locations.

On the basis of the data presented in our review, we recommend managing these lesions with complete local excision, similar to the intranasal papillomas. Conservative surgical management, as opposed to radical surgical intervention, is appropriate, followed by thorough examination afterward.

REFERENCES

1. Hyams VJ. Papillomas of the nasal cavity and paranasal sinuses. A clinicopathological study of 315 cases. Ann Otol Rhinol Laryngol 1971;80:192-206.

2. Weber RS, Shillitoe EJ, Robbins KT, et al. Prevalence of human papillomavirus in inverted nasal papillomas. Arch Otolaryngol Head Neck Surg 1988;114:23-6.

3. Brandwein M, Steinberg B, Thung S, Biller H, Dilorenzo T, Galli R. Human papillomavirus 6/11 and 16/18 in schneiderian inverted papillomas: in situ hybridization with human papillomavirus RNA probes. Cancer 1989;63:1708-13.

4. Beck JC, McClatchey KD, Lesperance MM, Esclamado RM, Carey TE, Bradford CR. Presence of human papillomavirus predicts recurrence of inverted papilloma. Otolaryngol Head Neck Surg 1995;113:49-55.

5. Beck JC, McClatchey KD, Lesperance MM, Esclamado RM, Carey TE, Bradford CR. Human papillomavirus types important in progression of inverted papilloma. Otolaryngol Head Neck Surg 1995;113:558-63.

6. MacDonald MR, Le KT, Freeman J, Hui MF, Cheung RK, Dosch HM. A majority of inverted sinonasal papillomas carries Epstein-Barr virus genomes. Cancer 1995;75:2307-12.

7. Astor FC, Donegan JO, Gluckman JL. Unusual anatomic presentations of inverting papilloma. Head Neck Surg 1985;7: 243-5.

8. Wolff AP, Ossoff RH, Clemis JD. Four unusual neoplasms of the nasopharynx. Otolaryngol Head Neck Surg 1980; 88:753-9.

9. O'Reilly BJ, Zuk R. Transitional cell papilloma of the nasopharynx. J Laryngol Otol 1989;103:528-30.

10. Fechner RE, Sessions RB. Inverted papilloma of the lacrimal sac, the paranasal sinuses and the cervical region. Cancer 1977;40:2303-8.

11. Schoub L, Timme AH, Uyss CJ. A well-differentiated inverted papilloma of the nasal space associated with lymph node metastases. S Afr Med J 1973;47:1663-5.

12. Nosanckuk JS. Oropharyngeal inverting papilloma. Arch Otolaryngol 1974;100:71-2.

13. Boesen PV, Laszewski MJ, Robinson RA, Dawson DE. Squamous cell carcinoma in an inverted papilloma of the buccal mucosa. Ann Otol Rhinol Laryngol 1991;100:748-50.

14. Hampal S, Hawthorne M. Hypopharyngeal inverted papilloma. J Laryngol Otol 1990;104:432-4.

15. Roberts WH, Dinges DL, Hanly MG. Inverted papilloma of the middle ear. Ann Otol Rhinol Laryngol 1993;102:890-2.

16. Stone DM, Berktold RE, Ranganathan C, Wiet RJ. Inverting papilloma of the middle ear and mastoid. Otolaryngol Head Neck Surg 1987;97:416-8.

17. Kaddour HS, Woodhead CJ. Transitional papilloma of the middle ear. J Laryngol Otol 1992;106:628-9.

18. Wenig BM. Schneiderian-type mucosal papillomas of the middle ear and mastoid. Ann Otol Rhinol Laryngol 1996;105: 226-33.

19. Anon JB, Rontal M, Zinreich SJ. Anatomy of the paranasal sinuses. New York, NY: Thieme Verlag, 1996:3-10.

20. Lawson W, Ho BT, Shaari CM, Biller HF. Inverted papilloma: a report of 112 cases. Laryngoscope 1995;105:282-8.

21. Vrabec DP. The inverted schneiderian papilloma: a 25 year study. Laryngoscope 1994;104:582-605.

22. Phillips PP, Gustafson RO, Facer GW. The clinical behavior of inverting papilloma of the nose and paranasal sinuses: report of 112 cases and review of the literature. Laryngoscope 1990;100:463-9.

Ann Otol Rhinol Laryngol 108:1999

QUANTITATIVE STUDY OF GERMINAL CENTER AREA IN NORMAL AND DISEASED TONSILS USING IMAGE ANALYSIS

JANET L. GORFIEN, MA
BERNICE NOBLE, PHD
ROBERT HARD, PHD
LINDA BRODSKY, MD
BUFFALO, NEW YORK

The aim of this study was to measure the germinal center area of secondary follicles in a consistent and unbiased manner using image analysis. Tonsil specimens were obtained from children with clinical evidence of recurrent tonsillitis and/or idiopathic tonsillar hypertrophy. Normal control biopsy specimens were obtained from children with no history of ear, nose, or throat infections. The results show a significant increase in the germinal center area in tonsils exhibiting hypertrophy when compared to normal controls ($p < .002$). Image analysis is an important tool for making quantitative size comparisons in lymphoid tissues.

KEY WORDS — germinal center area, image analysis, tonsil, tonsillar hypertrophy.

INTRODUCTION

Tonsillectomy is one of the most common pediatric operations performed in the United States, and obstructive hyperplasia is the most frequent indication for removal of the palatine tonsils. On gross examination, these tonsils are very large, and can occupy more than 75% of the oropharyngeal airway.[1] Brodsky et al[2] compared tonsil sizes (weight/volume) from patients with recurrent tonsillitis with and without hypertrophy, and with idiopathic tonsillar hypertrophy, and found that tonsils from patients exhibiting hypertrophy were significantly larger than tonsils from patients with recurrent tonsillitis alone.

Normal palatine tonsils are surrounded by a layer of stratified squamous epithelium that extends into deep, branching crypts.[3] Within these crypts, numerous lymphocytes and other nonepithelial cells infiltrate the epithelium, which is referred to as reticular epithelium. Numerous primary and secondary lymphoid follicles can be observed underlying the epithelial layer, and the number of these follicles is dependent on the current immunologic activation state of the tonsil. Germinal centers, consisting primarily of B cells, are located within the secondary lymphoid follicles. The area in between the lymphoid follicles is referred to as the extrafollicular area, and is primarily an area of T cell concentration, although other cell types are also found in this region.

To elucidate the etiology of tonsillar hypertrophy, it is important to determine whether the microanatomic architecture of hypertrophic tonsils differs significantly from that of tonsils exhibiting no hypertrophy. Favre et al[4] found an increase in lymphoid elements as opposed to connective tissue stroma in tonsils exhibiting hypertrophy. Brodsky et al[5] demonstrated an increase in the number of B cells, helper T cells, and suppressor T cells in hypertrophic tonsils compared to normal controls. Antigen-presenting cells were also increased with disease compared to normal controls.[6] There appears to be an increase in some cell populations within the hypertrophic tonsil. However, the location or histologic compartment in which these cells reside has not been analyzed in detail. It has been suggested that hypertrophic tonsils exhibit increased follicle size. Using the point-counting method, Surjan et al[7] estimated germinal center size and concluded that germinal centers were enlarged in hypertrophic tonsils compared to those from patients with recurrent tonsillitis. However, no information was provided to establish the statistical significance of that observation.

Image analysis has been used for many years to compare morphometric features of normal versus diseased tissues.[8] The power of this approach has been extended considerably by video acquisition, enhancement, and analysis techniques.[9] In the present study, we used image analysis to measure the area of germinal centers in both normal and diseased tonsil tissue. To our knowledge, these measurements have not been performed previously in a consistent and unbiased manner. Results will allow comparison of germinal center areas between well-established clinical categories and normal biopsy controls.

MATERIALS AND METHODS

Tonsil Specimens. Tonsil tissue was obtained from

From the Departments of Microbiology (Gorfien, Noble), Anatomy (Hard), Otolaryngology (Brodsky), and Pediatrics (Brodsky), State University of New York at Buffalo, School of Medicine and Biomedical Sciences, and Children's Hospital of Buffalo, Buffalo, New York.

CORRESPONDENCE — Bernice Noble, PhD, State University of New York at Buffalo, Dept of Microbiology, 242 Cary Hall, 3435 Main St, Buffalo, NY 14214.

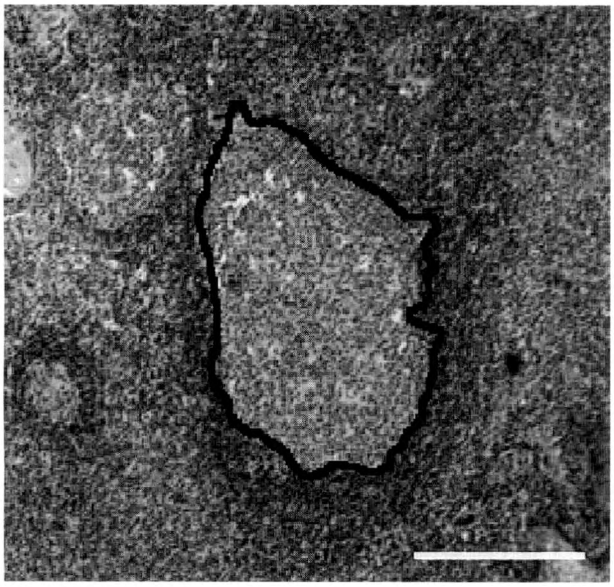


Fig 1. Digitized image of germinal center from secondary follicle (original ×6.25). Black outline indicates area measured. Bar — 300 μm.

children who underwent tonsillectomy for recurrent bouts of acute tonsillitis and/or obstructive tonsillar hyperplasia. The average age of patients was 7 years (SD 3 years; range 2 years 7 months to 13 years 8 months) for both the entire patient population and patients who were randomly selected to be in the final study group. The male-to-female ratio of the entire population was 57:43, and the ratio of the patients in the final study group was 50:50.

Three clinical classifications were established based on both the estimated tonsil size and the presence of a clinical history of infection: 1) recurrent tonsillitis (RT), for tonsils small in size (0 or 1+) with a history of greater than 4 bouts of acute tonsillitis per year for more than 1 year; 2) recurrent tonsillitis with hypertrophy (RT/H), for tonsils very large in size (3+ or 4+) with the same history as those patients with recurrent tonsillitis; 3) idiopathic tonsillar hypertrophy (ITH), for tonsils very large in size (3+ or 4+) with no history of infection.[2,5] Bacteriology findings were as described earlier by Brodsky et al.[2,5] *Haemophilus influenzae* (HI) was isolated as the dominant microorganism in hypertrophic tonsils, whereas HI was rarely cultured as the dominant microorganism in tonsils from patients with RT. Normal tonsil biopsy specimens of core tonsil tissue were obtained from children undergoing surgery for noninfectious otolaryngological problems. These children had no previous history of ear, nose, and throat disease, and none had taken antibiotics for 6 months prior to surgery. On physical examination, their tonsils were small in size and normal in appearance. The study was approved by the Institutional Review Board of the Children's Hospital of Buffalo; participation required informed parental consent.

Histology. Tonsil tissue was placed in 10% neutral buffered formalin for either 24 hours (RT, RT/H, and ITH) or 4 hours (small control specimens). Tissues were subsequently washed, routinely processed, and embedded in paraffin. Tissue sections were cut to 4-μm thickness, placed on Histostick-coated slides (Accurate, Westbury, NY), and incubated in a 60°C oven for 1 hour. Sections were routinely stained with Harris hematoxylin and eosin for morphological evaluation.

Quantitative Image Analysis. Analysis was limited by the number of control specimens ($n = 8$). One slide with 4 sections was prepared for each specimen. A section on each slide was randomly selected with a random number-generating algorithm. For each of the other clinical groups, 8 specimens were randomly chosen, from which 1 section was randomly selected, as described above for the controls.

Each section was imaged with a Zeiss stereoscope and collected with a Dage Newvicon video camera. Images were digitized with a Perceptics Pixel Pipeline digitizing board housed in a MacIntosh Quadra 950 microcomputer operating with Oncor Image software and saved to a disk. All secondary follicles in each image were labeled. Since the control sections were small, every secondary follicle in the control sections was selected for analysis. Each section from the other clinical categories was matched randomly to one of the control sections, and the same number of secondary follicles was randomly selected as in the matched control section.

Each section was examined at higher resolution with a Zeiss Axioskop microscope equipped with a 5× objective (numerical aperture [NA] = 0.15) and a low NA condenser (NA = 0.9). Contrast was enhanced with a narrowband green filter. Images were acquired with a Paultek Cooled CCD camera and analog-processed so as to obtain full 8-bit gray values. Images again were digitized with a Perceptics Pixel Pipeline digitizing board housed in a MacIntosh Quadra 950 microcomputer operating with Oncor Image software.

Investigators measuring germinal center area were blinded to patient clinical category for all disease groups. As indicated earlier, normal tonsil biopsy specimens were small and could be identified by visual inspection; however, all determinants of measurement were previously chosen by a random selection process using a random number-generating algorithm.

A macro program was written for automated or

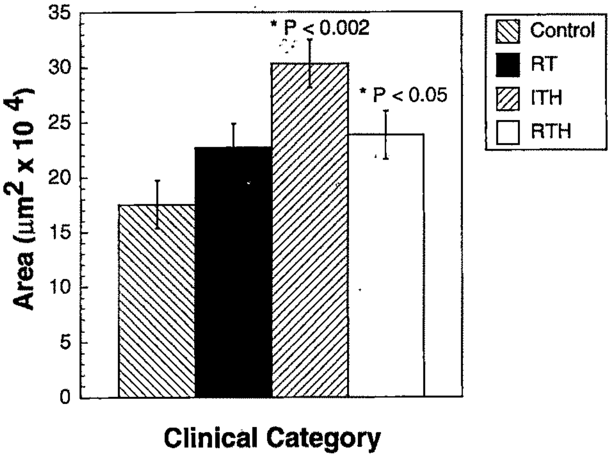


Fig 2. Bar chart comparing mean area measurements for all patient groups. Idiopathic tonsillar hypertrophy (ITH) and recurrent tonsillitis with hypertrophy (RTH) groups are significantly different from control group ($p < .002$ and $p < .05$, respectively). RT — recurrent tonsillitis.

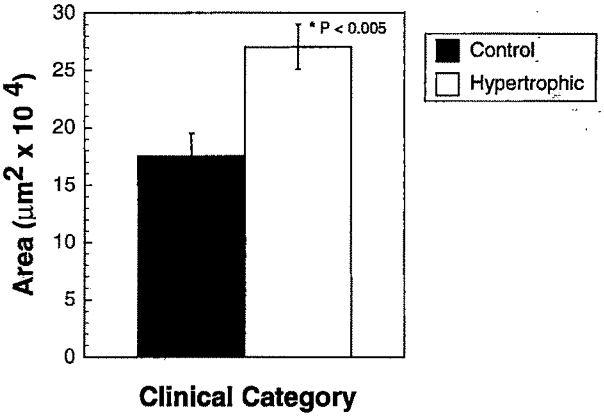


Fig 3. Bar chart comparing mean area measurements for normal control group versus all hypertrophic tonsils. Hypertrophic groups are significantly different from control group ($p < .005$).

manual thresholding of the germinal centers of each secondary follicle and calculation of germinal center area. Distance was determined with a stage micrometer. The mean ± standard error was determined for each clinical category, and an unpaired Student's *t*-test was used for statistical analysis.

RESULTS

Germinal centers were easily distinguished from mantle zones in all follicles (Fig 1). Comparisons were made of germinal center area measurements between clinical groups and normal controls. A total of 45 germinal centers was measured for each clinical group. Figure 2 shows the mean area measurements for all patient groups. Normal controls had the smallest germinal center areas (175,118 μm^2, range 25,789 to 641,479 μm^2), while RT, RT/H, and ITH disease groups all had larger germinal center areas (226,694, 238,270, and 302,861 μm^2, respectively). Both the ITH and RT/H groups were significantly different from the control group ($p < .002$ and $p < .05$, respectively). Tonsils from RT patients had the smallest germinal center area measurements of the disease groups. There were no statistically significant differences between RT and hypertrophic groups. When the 2 hypertrophic clinical categories (ITH and RT/H) were combined and compared to the control group, they were significantly different from the control group ($p < .005$; Fig 3). Figure 4 depicts representative samples from each patient group.

DISCUSSION

The purpose of the germinal center measurements in this study was to compare tonsils from patients in different clinical categories. No attempt was made to measure the absolute size of the germinal centers. There have been only a few reports that attempt to determine relative germinal center size in secondary follicles. Brandtzaeg et al[10] estimated germinal center size using the point counting method in examining normal tonsil biopsy specimens from individuals of different ages, and found that younger individuals (4 to 25 years old) had slightly larger germinal centers than older individuals (30 to 81 years old). However, this difference was not statistically significant, and no comparison of normal and diseased tonsil tissue was reported in that study. In the older point-counting method, an ocular grid was placed over a tissue section, and the number of cross points on the grid overlying each tissue compartment was counted and compared with the number corresponding to the entire section area. Computer analysis of digitized, thresholded images provided much more rapid and accurate estimates of area. Crocker et al,[11] using image analysis to measure germinal center size in lymph nodes from patients with follicular lymphoma and reactive follicular hyperplasia, found that germinal centers in lymph nodes with follicular hyperplasia were significantly larger. Although those investigations included the examination of several tonsils, the tonsils were not classified by clinical disease category, nor were normal tissues studied for comparison.

The data reported here show that hypertrophic tonsils exhibit significantly larger germinal centers when compared to normal controls. Our findings support the results of Surjan et al,[7] which indicated that germinal centers from hypertrophic tonsils were enlarged compared to tonsils from patients with RT.

The cause of tonsillar hypertrophy is largely unknown. It has been suggested that the bacteriology of hypertrophic tonsils may differ from that of ton-

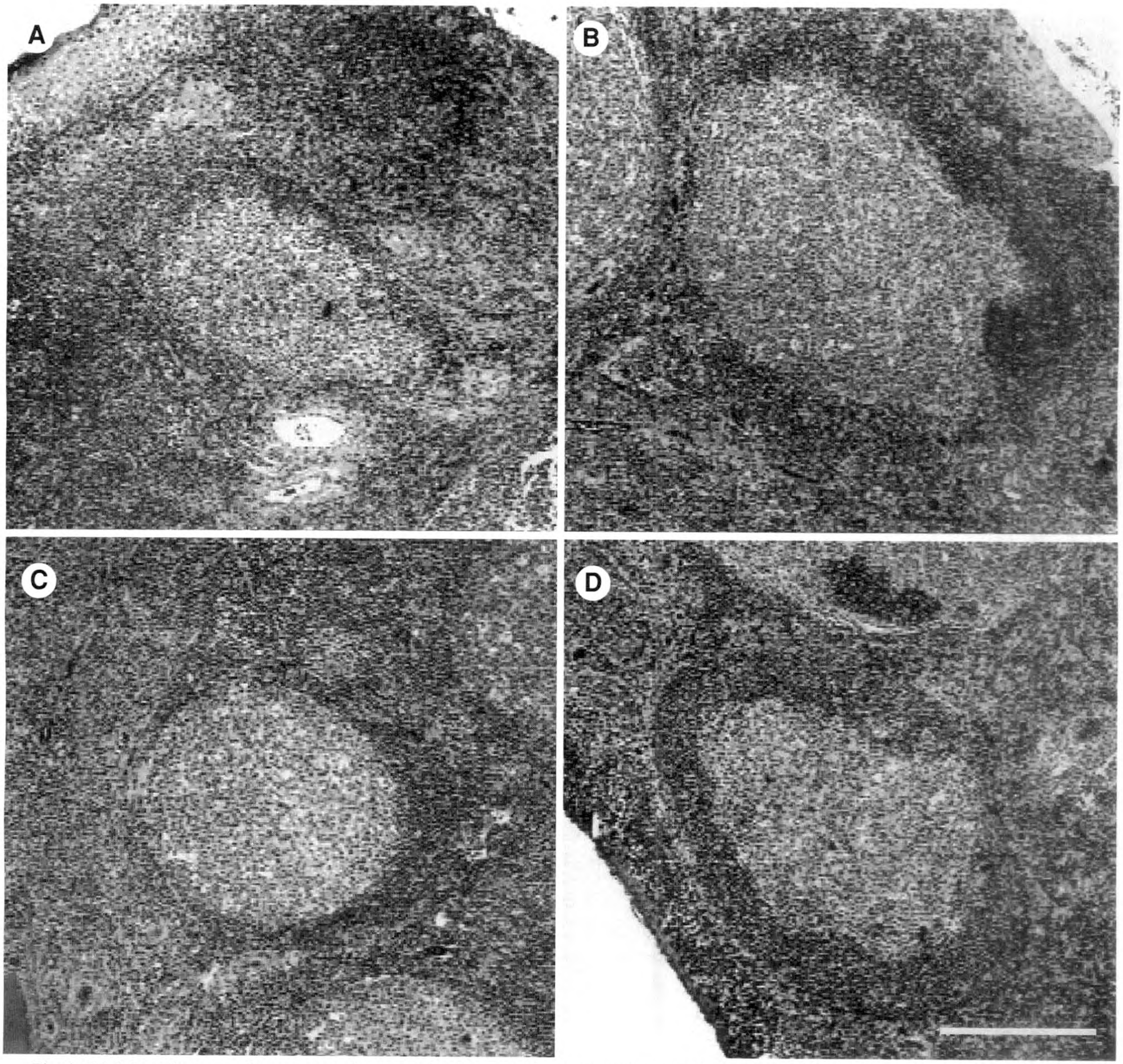


Fig 4. Digitized images of representative germinal centers from normal controls and diseased tonsil groups (original ×6.25). Bar — 300 μm. A) Normal control biopsy. B) Idiopathic tonsillar hypertrophy. C) Recurrent tonsillitis. D) Recurrent tonsillitis with hypertrophy.

sils exhibiting chronic infection alone.[2] *Haemophilus influenzae* appears to play a significant role in the development of tonsillar hypertrophy; HI bacterial load has been positively correlated with tonsil weight. Further, when HI was the dominant bacterial species isolated from a tonsil, there was a concomitant increase in the number of antigen-presenting cells in the surface and crypt epithelia.[6] Brodsky et al[5] observed an increase in the number of B cells in hypertrophic tonsils when compared to normal controls; the number of B cells was correlated with the presence of HI as the dominant bacterial species. The results described here support those findings. Germinal centers contain mainly B cells, and germinal center area measurements were the greatest in tonsils exhibiting hypertrophy.

Koch and Brodsky[12] postulated that tonsillar tissue lymphocytes in diseased tonsils may be preactivated by the dominant bacterium, resulting in an immunologic or hyperplastic response. They also presented evidence that lymphocytes from diseased tonsils become refractory or tolerant to immune activation by certain pathogens associated with tonsillar disease. Whether or not these mechanisms are responsible for increased cellularity of germinal centers remains to be determined. However, it does appear that B lymphocyte proliferation contributes substantially in the physical mechanism for tonsillar hypertrophy.

ACKNOWLEDGMENT — We thank the Histology Laboratory at the State University of New York at Buffalo School of Medicine and Biomedical Sciences for tissue processing and staining of tonsillar tissues.

REFERENCES

1. Brandtzaeg P. Immune functions and immunopathology of palatine and nasopharyngeal tonsils. In: Bernstein J, Ogra P, eds. Immunology of the ear. New York, NY: Raven Press, 1987: 63-106.
2. Brodsky L, Moore L, Stanievich J. The role of *Haemophilus influenzae* in the pathogenesis of tonsillar hypertrophy in children. Laryngoscope 1988;98:1055-60.
3. Perry ME, Jones MM, Mustafa Y. Structure of the crypt epithelium in human palatine tonsils. Acta Otolaryngol Suppl (Stockh) 1988(suppl 454):53-9.
4. Favre A, Paoli D, Poletti M, Pesce G, Giampalmo A, Rossi F. The human palatine tonsil studied from surgical specimens at all ages and in various pathological conditions. I. Morphological and structural analyses. J Mikrosk Anat Forsch 1986; 100:7-33.
5. Brodsky L, Moore L, Stanievich J, Ogra PL. The immunology of tonsils in children: the effect of bacterial load on the presence of B- and T-cell subsets. Laryngoscope 1988;98:93-8.
6. Brodsky L, Frankel SS, Gorfien J, Rosman J, Noble B. The role of dendritic cells in the development of chronic tonsillar disease in children. Acta Otolaryngol Suppl (Stockh) 1996 (suppl 523):98-100.
7. Surjan L, Brandtzaeg P, Berdal P. Immunoglobulin systems of human tonsils. Clin Exp Immunol 1978;31:382-90.
8. Loud AV, Anversen P. Biology of disease. Morphometric analysis of biologic processes. Lab Invest 1984;50:258-61.
9. Russ JC. The image processing handbook. Boca Raton, Fla: CRC Press, 1995.
10. Brandtzaeg P, Surjan L, Berdal P. Immunoglobulin systems of human tonsils. 1. Control subjects of various ages: quantification of Ig-producing cells, tonsillar morphometry and serum Ig concentrations. Clin Exp Immunol 1978;31:367-81.
11. Crocker J, Jones EL, Curran RC. A quantitative study of the size of benign and malignant lymphoid follicles. J Clin Pathol 1983;36:1055-61.
12. Koch RJ, Brodsky L. Effect of specific bacteria on lymphocyte proliferation in diseased and nondiseased tonsils. Laryngoscope 1993;103:1020-6.

≈

RECENT ADVANCES IN OTITIS MEDIA

The 7th International Symposium on Recent Advances in Otitis Media will be held June 1-5, 1999, in Fort Lauderdale, Florida. For information, contact David J. Lim, MD, House Ear Institute, 2100 W Third St, Los Angeles, CA 90057.

Ann Otol Rhinol Laryngol 108:1999

SEVERE COMBINED IMMUNODEFICIENCY: OTOLARYNGOLOGICAL PRESENTATION AND MANAGEMENT

ROSE MARY S. STOCKS, MD, PHARMD
MEMPHIS, TENNESSEE

JEROME W. THOMPSON, MD, MBA
MEMPHIS, TENNESSEE

JOSEPH A. CHURCH, MD
LOS ANGELES, CALIFORNIA

SHEILA KUN, RN, MS
LOS ANGELES, CALIFORNIA

ERIN SIMMS, MD
MEMPHIS, TENNESSEE

In order to increase the awareness of otolaryngologists of severe combined immunodeficiency syndrome (SCIDS) so they may contribute to an earlier diagnosis of this disorder, we performed a retrospective chart review of a multicenter series from 2 children's hospital medical centers. Eighteen cases were identified, and 14 had an otolaryngological presentation. The average age of presentation was 3.3 months, and 72% were males. Most cases were inherited in an X-linked fashion. Five patients had thrush; 4 had recurrent otitis media. Other otolaryngological presentations included cough, mouth ulcers, pharyngitis, mastoiditis, and bilateral neck abscess. The most severe form of immunodeficiency, SCIDS is a rare condition that involves a disorder in both T and B cell functions. The manifestations involving the head and neck include recurrent upper respiratory tract infections, otitis media, thrush, oral ulcers, and abscesses. It is important that SCIDS be considered in any infant with recurrences of these common infections.

KEY WORDS — abscess, mastoiditis, severe combined immunodeficiency syndrome.

INTRODUCTION

Severe combined immunodeficiency syndrome (SCIDS) represents a group of heterogeneous disorders characterized by a deficiency in the development or function of B and T lymphocytes, profound lymphopenia, and deficient humoral and cell-mediated immunity.[1-4] The most severe form of immunodeficiency, SCIDS is transmitted by X-linked and autosomal recessive patterns of inheritance.[1,3] Otolaryngologists often provide the first care for these children, who present with recurrent upper respiratory tract infections, otitis media, and cough. This may be the earliest manifestation of their altered immune status.[2] Recurrent infections in an infant should raise the clinician's suspicion of potential defects in the patient's immune system. We describe 18 cases of SCIDS, of which 70% had an initial otolaryngological presentation.

RESULTS

Eighteen children were identified with SCIDS at LeBonheur Children's Medical Center in Memphis, Tennessee, and at Children's Hospital of Los Angeles for the years 1977 to 1997, and a retrospective chart review was performed. Each patient had profound deficiencies of T and B cell functions and fulfilled the criteria of the World Health Organization for lymphopenic combined immunodeficiency.[5] This excluded patients with acquired immunodeficiencies caused by human immunodeficiency viruses, as well as DiGeorge's anomaly with thymic aplasia.

Thirteen of the 18 infants with SCIDS were boys, and 5 were girls. The mean age at diagnosis was 3.3 months and did not differ significantly among the different genetic types. Except for those whose disease was diagnosed prenatally or at birth because of a previously affected family member, the clinical presentations were similar to those in previous surveys.[4] The 18 patients are described in the Table according to family history, sex, age at diagnosis, treatment, and clinical manifestations.

DISCUSSION

Severe combined immunodeficiency syndrome is the most severe form of congenital immunodeficiency. This includes a spectrum of diseases with defects in the development or function of both B and T lymphocytes resulting in defective humoral and cell-mediated immunity. The genetic origins of SCIDS are diverse.[4] The diseases in this category are inherited in an X-linked and autosomal recessive fash-

---

From the Department of Otolaryngology–Head and Neck Surgery, University of Tennessee, Memphis, and LeBonheur Children's Medical Center, Memphis, Tennessee (Stocks, Thompson, Simms), and the Department of Otolaryngology, Children's Hospital of Los Angeles, Los Angeles, California (Church, Kun).

Presented at the meeting of the American Society of Pediatric Otolaryngology, Scottsdale, Arizona, May 14-16, 1997.

CORRESPONDENCE — Rose Mary S. Stocks, MD, PharmD, 777 Washington, P-110, Memphis, TN 38105.

SUMMARY OF PATIENTS

Patient	*Age at Diagnosis*	*Sex*	*Family History*	*Type of SCIDS*	*Documented Absence of Tonsils and Thymus*	*Otolaryngological Presentation*	*Other Presentations*
1	3 mo	M		X-linked	+	Nasal congestion, frequent upper respiratory tract infections, painful mouth ulceration, thrush	Pneumonia
2	19 d*	M	+			Nasal congestion*	*
3	5$^1/_2$ mo	M		X-linked		Cough, perioral cyanosis	Pneumonia
4	8 mo	F		Not determined		Otitis media	Pneumonia
5	5 mo	M		X-linked		Cough	Pneumonia
6	1 mo*	M	+	Adenosine deaminase deficiency		Mouth ulcers, cough*	Pneumonia, rash, fever, diarrhea, weight loss*
7	6 wk	F		Adenosine deaminase deficiency	+	Bilateral cervical abscess	Diarrhea, failure to thrive
8	6 wk	M	+	X-linked	+	Thrush	
9	4 mo	M		X-linked		Upper respiratory tract infection, thrush	
10	7 mo	M	+	X-linked			Diarrhea, failure to thrive
11†	5 mo	F		Autosomal recessive	+	Otitis media, pharyngitis, upper respiratory tract infection, thrush	Pneumonia
12†	Prenatal diagnosis*	M	+	Autosomal recessive		*	*
13	2$^1/_2$ mo	M		X-linked	+	Otitis media	Rash, pustules
14	2$^1/_2$ mo	M		X-linked	+	Otitis media	Rash
15†	8 mo	F		Autosomal recessive			Pneumonia, rash
16	Birth	M	+	X-linked			Pneumonia, rash
17	3 mo	F		Adenosine deaminase deficiency		Mastoiditis	Pneumonia, rash, osteocellulitis
18	1$^1/_2$ mo	M		Adenosine deaminase deficiency		Rhinorrhea, thrush	Pneumonia, rash

All patients had bone marrow transplants — twice in patient 4, and 3 times in patient 12.

*Limited symptoms due to prenatal diagnosis or suspected diagnosis.

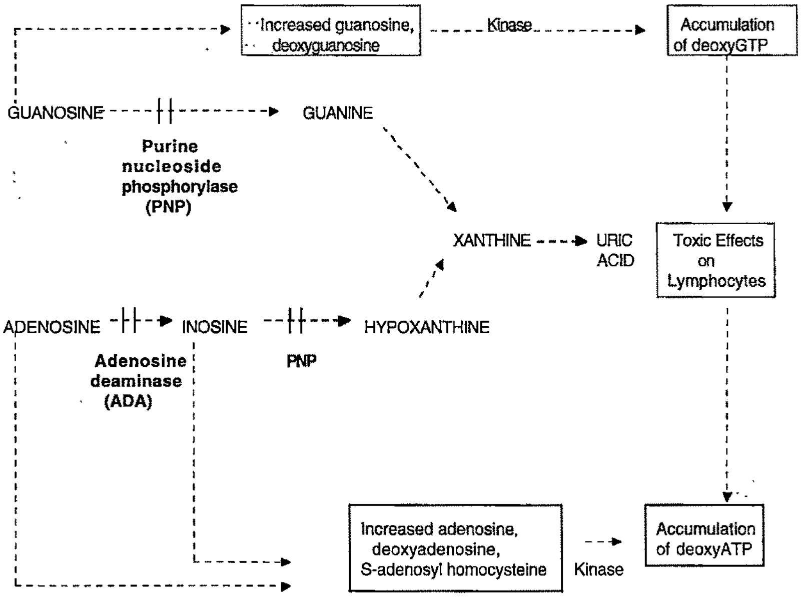
†Metaphyseal chondrodysplasia, McKusick type (cartilage-hair-hypoplasia syndrome).

ion.[1,3,6]

The incidence of SCIDS is between 1 in 30,000 and 1 in 500,000 live births.[2,4,7] The thymus and peripheral lymphoid organs of these patients, such as the tonsils and lymph nodes, contain few or no lymphocytes and may be absent or hypoplastic.[6,7] These infants have very low blood lymphocyte counts, absent mitogen responses, and absent or decreased antibody titers, as well as generally low serum immunoglobulins and a poor antibody response.[6,8] Approximately 75% of these infants are male.[1,3,8] There is marked heterogeneity in the phenotypes of circulating lymphocytes, which is probably due to the diverse genetic causes.[4] The most useful screening diagnostic test is the absolute lymphocyte count.[4]

The usual presentation of SCIDS is persistent oral candidiasis, severe diarrhea, otitis media, and cough secondary to interstitial pneumonia, frequently caused by *Pneumocystis carinii* and/or cytomegalovirus during the first 1 to 2 months of life.[1,3,9] All of the cases with pneumonia in our series were caused by *P carinii*. Initially, the growth of these children is normal; however, within several months after birth, the patients begin to drop below the normal growth curves and develop failure to thrive.[1,2]

The ear, nose, and throat manifestations of SCIDS are recurrent suppurative otitis media, tonsillitis, si-


Increased guanosine, deoxyguanosine
Kinase
Accumulation of deoxyGTP
GUANOSINE
GUANINE
Purine nucleoside phosphorylase (PNP)
XANTHINE
URIC ACID
Toxic Effects on Lymphocytes
ADENOSINE
INOSINE
HYPOXANTHINE
Adenosine deaminase (ADA)
PNP
Increased adenosine, deoxyadenosine, S-adenosyl homocysteine
Kinase
Accumulation of deoxyATP

Congenital defects in purine metabolism.

nusitis, rhinitis, and adenoiditis.[2] Over 70% of the cases in our series had an otolaryngological presentation prior to the diagnosis. Other presentations noted in our patient data included mouth ulcers, nasal congestion, pharyngitis, cough, and thrush. Complications from this disorder may lead to chronic otorrhea, mastoiditis, osteomyelitis, and cervical neck abscesses.[2] Because of their defective immune system, these patients are susceptible to recurrent episodes of sepsis and severe bacterial, viral, fungal, and protozoal infections.[2,9]

A majority of the cases of SCIDS are inherited in an X-linked fashion due to a defective gene in the X chromosome.[8] Mutations in the gene that encodes for the γ chain of the interleukin (IL) receptor are associated with the X-linked forms of SCIDS.[3,6] The γ chain of IL-2R is also a common component for the IL-4 and IL-7 receptors. Three interleukins — IL-2, IL-4, and IL-7 — are essential in the various stages of growth and development of T and B cells.[3] Over one third of these cases represent the first manifestation of a new mutation.[8] It may not be possible to distinguish clinically between the X-linked forms and the autosomal recessive forms.[8]

Approximately half of the autosomal recessive forms of SCIDS are due to a deficiency in the enzyme adenosine deaminase (ADA).[3] Absence of this enzyme leads to the accumulation of various toxic metabolites, including deoxyadenosine, deoxyadenosine triphosphate, and S-adenosyl homocysteine, in developing T and B lymphocytes[6] (see Figure). These metabolites block the DNA synthesis and are toxic to lymphocytes. This blockage causes the accumulation of compounds that inhibit the transmethylation reactions, thus reducing the numbers of B and T cells.[6] The ADA form accounts for about 20% of all cases of SCIDS.[1,6,9] The ADA gene has been mapped on chromosome 20q13-ter and has been cloned.[2,6]

The clinical manifestations of deaminase (ADA) SCIDS are similar to those of non-ADA SCIDS.[9] However, ADA-deficient patients will have skeletal abnormalities, primarily of the rib cage and scapula. These include flaring of the anterior ribs and deformities of the transverse process of the vertebrae and scapula. The skin color may be extremely ruddy because of the accumulation of adenosine, which is a potent vasodilator.[9] The diagnosis of this disorder is made by the measurement of ADA levels in hemolyzed red blood cells.[1] The prenatal diagnosis can be made during the second trimester of pregnancy by assaying ADA levels in cultured amniotic cells.[3]

A rarer form of the autosomal recessive disorder of SCIDS is due to the deficiency of purine nucleoside phosphorylase (PNP), which is involved in the metabolism of purines. Only 33 cases have been reported in the literature.[10,11] This disorder is associated with severe cell-mediated immunodeficiency with an intact humoral immunity and is mapped to chromosome 14q13.1.[3,10] Because of the intact humoral immunity, which is variable, some view PNP as an immune deficiency of T cells and not representative of SCIDS.[4] The accumulation of deoxyguanosine and deoxyguanosine triphosphate has a toxic effect primarily on T cells[1,6] (see Figure). Two thirds of these patients will have evidence of various neurologic disorders ranging from a mild developmental delay to mental retardation.[3] The measurement of PNP from hemolyzed red blood cells confirms the diagnosis. Also, a normal uric acid level can help rule out the disease, since a low serum uric acid level is a result of the absence of this enzyme.[1,3] During the second trimester, the prenatal diagnosis can be made by assaying the PNP levels in cultured amniotic cells.[3]

Other autosomal recessive forms of SCIDS have been recognized recently.[9] The bare lymphocytes syndrome is one that has a deficiency in class II major histocompatibility complex expression. In these patients, the defect is usually due to abnormalities of the DNA binding protein, which is either reduced or structurally abnormal and rendered inactive. The affected individual is deficient in the antibody responses to T-dependent protein antigens and is susceptible to infections.[6] Another form includes the deficiency of ZAP-70, which is a protein kinase.[3] ZAP-70 maps to chromosome 2q12.[3] Omenn syndrome is characterized by a maturation defect in the T and B cells, as well as increased IgE.[7,12]

Cases 11, 12, and 15 have the syndrome metaphyseal chondrodysplasia, McKusick type, which is also known as cartilage-hair-hypoplasia syndrome.[13,14] Severe combined immunodeficiency syndrome has been associated with this syndrome. The cause of SCIDS in these patients is an intrinsic defect causing defective proliferation of T cells and B cells.[14] The disorder was first recognized in the Amish population; however, subsequently, it was detected in other groups. These patients typically are short-limbed dwarfs with sparse body hair.[13,14] There is also an association of malignancies, esophageal atresia, Hirschsprung's disease, and congenital hypoplastic anemia.[13]

Without therapy, infants with SCIDS usually die of overwhelming infections during the first year of life. Until recently, the treatment available for these patients was limited. Fetal liver transplantation and fetal thymus transplantation yielded poor results.[2,7] Because of the routine utilization of irradiated blood products that cause reduction in transfusion-induced graft-versus-host disease, and utilization of improved antibiotics, the incidence of death before bone marrow transplantation has decreased. Currently, bone marrow transplantation offers the greatest chance to correct the immune defect in SCIDS.[2,9] It is the treatment of choice when there is a histocompatible sibling donor.[2,9]

Gene therapy is a new technique that is being utilized now for the treatment of SCIDS. The first human trials of gene therapy were conducted in the early 1990s. This was done by inserting the gene for ADA into the peripheral white blood cells to treat children with ADA-deficiency SCIDS.[9] In 1993, 3 infants with ADA-deficient SCIDS received genetically altered hemopoietic stem cells that had been collected from umbilical cord blood at the time of birth.[3,9] Now, the diagnosis of ADA-deficient SCIDS and PNP-deficient SCIDS can be made prenatally by amniocentesis or chorionic villus sampling. Also, the prenatal diagnosis of autosomal recessive SCIDS can be made by fetal blood sampling at 20 weeks' gestation through enumeration of lymphocyte subsets and functional studies.[3] One study noted improvement in the immunologic function of PNP-deficient T lymphoid cells with retroviral-mediated gene transfer.[10] Not long ago, in Chicago, a fetal bone marrow transplant was performed for a prenatal diagnosis of SCIDS.

CONCLUSION

Eighteen cases of SCIDS are presented. Two thirds presented with otolaryngological symptoms prior to the laboratory diagnosis of SCIDS. Only 1 case was diagnosed by an otolaryngologist, even though a majority had been seen by an otolaryngologist. The purpose of this paper is to increase the awareness of otolaryngologists of this disorder so that they can make an earlier diagnosis in these children and increase survival with immediate therapy.

REFERENCES

1. Shyur SD, Hill H. Immunodeficiency in the 1990s. Pediatr Infect Dis J 1991;10:595-611.

2. Harris JP, South MA. Immunodeficiency diseases: head and neck manifestations. Head Neck Surg 1982;5:114-24.

3. Shyur S, Hill HR. Recent advances in the genetics of primary immunodeficiency syndromes. J Pediatr 1996;129:8-24.

4. Buckley RH, Schiff RI, Schiff SE, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 1997;130: 378-87.

5. WHO Scientific Group. Primary immunodeficiency diseases; report of a WHO scientific group. Clin Exp Immunol 1995;99:1-24.

6. Abbas AK, Lichtman AH, Pober JS. Cellular and molecular immunology. Philadelphia, Pa: WB Saunders, 1994:411-29.

7. Stephan JL, Vlekova V, Le Deist F, et al. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. J Pediatr 1993;123:564-72.

8. Puck JM. Prenatal diagnosis and genetic analysis of X-linked immunodeficiency disorders. Pediatr Res 1993;33(suppl):S29-S34.

9. Noonan NA, Senner AM. Gene therapy techniques in the treatment of adenosine deaminase deficiency–severe combined deficiency syndrome. J Perinat Neonatal Nurs 1994;7:65-78.

10. Nelson DM, Butters KA, Markert ML, Reinsmoen NL, McIvor RS. Correction of proliferative responses in purine nucleoside phosphorylase (PNP)–deficient T lymphocytes by retroviral-mediated PNP gene transfer and expression. J Immunol 1995;154:3006-14.

11. Markert ML, Hershfield MS, Schiff RI, Buckley RH. Adenosine deaminase and purine nucleoside phosphorylase deficiencies: evaluation of therapeutic intervention in eight patients. J Clin Immunol 1987;7:389-99.

12. Locksley RM, Wilson CB. Cell mediated immunity and its role in host defense. In: Mandel GI, ed. Principles and practices of infectious diseases. 4th ed. New York, NY: Churchill Livingstone, 1995:102-48.

13. Jones KL. Osteochondrodysplasia. In: Smith's recognizable patterns of human malformation. 5th ed. Philadelphia, Pa: WB Saunders, 1997:384-5.

14. McKusick VA. Autosomal recessive phenotypes. In: Francomano CA, Antonarakis SE, Pearson PL, eds. Mendelian inheritance in man. 9th ed. Baltimore, Md: Johns Hopkins Press, 1995:1322-3.

≈

FUNCTIONAL AESTHETIC NASAL SURGERY

The 17th International Course in Functional Aesthetic Nasal Surgery will be held in English, June 15-18, 1999, in Utrecht, the Netherlands. For information, contact Ms. T. Kortleve, Dept of ORL, University Hospital Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands; telephone +31-30-2506645; fax +31-30-2541922; e-mail t.kortleve@kmb.azu.nl.

Ann Otol Rhinol Laryngol 108:1999

IMAGING CASE STUDY OF THE MONTH

ENDOSCOPIC MANAGEMENT OF LATERAL PHARYNGEAL POUCH

PATTI C. HUANG, MD RICHARD L. SCHER, MD
DURHAM, NORTH CAROLINA

INTRODUCTION

Lateral pharyngeal pouches and true lateral pharyngeal diverticula represent protrusions most commonly involving the area between the middle and inferior constrictors through the thyrohyoid membrane.[1] They are rarely considered in the differential diagnosis of dysphagia. Clinical manifestations may include regurgitation of undigested food, throat irritation, hoarseness, and worsening pulmonary symptoms. However, many patients remain asymptomatic. Lateral pharyngeal pouches may not be as uncommon as indicated in the previous literature.

We describe a patient with a lateral pharyngeal pouch, as well as a novel variation for treatment. The surgical technique derives from the evolution of treatment of Zenker's diverticulum.[2,3] Modification of the endoscopic approach with an endosurgical stapler creates a "sutured" closure of the mucosal edges formed during division of the common wall.

CASE REPORT

A 70-year-old woman with a past medical history including reactive airway disease and chronic bronchitis presented with a several-year history of dysphagia. During the past year, she was noted to have several episodes of bronchitis and pneumonia. Due to her deteriorating pulmonary status, she was subsequently referred to our otolaryngology department for evaluation of her symptoms of dysphagia. A diagnosis of Zenker's diverticulum was suspected.

The patient reported regurgitation of undigested food, choking during eating, and worsening pulmonary symptoms. She also stated that placement of her left hand on her neck while eating did prevent the sensation of food becoming lodged in her throat.

Head and neck examination revealed no gross abnormalities. Pooling of secretions was noted in the left pharyngeal area. A barium swallow study revealed a left-sided pharyngeal pouch with retention of barium in the sac (Fig 1).

The patient underwent direct laryngoscopy in the operating room. A pouch was identified in the left lateral pharynx, adjacent to the vallecula (Fig 2A). Endoscopic stapling of a mucosal band was performed, with marked improvement in symptoms and pulmonary status.

The patient was admitted on the morning of surgery. The procedure was performed with the patient under general anesthesia with muscle relaxants. The patient was placed in the supine position with the head in extension as for routine rigid laryngoscopy. A Weerda laryngoscope was introduced toward the left pyriform sinus. A common wall between the pharyngeal pouch and the pharynx was identified along the lateral aspect. The laryngoscope was suspended with the distal crossbar of the suspension apparatus resting on a Mayo stand. The pouch was then closely inspected with rigid telescopes attached to a video camera.

The common wall between the pouch and the phar-

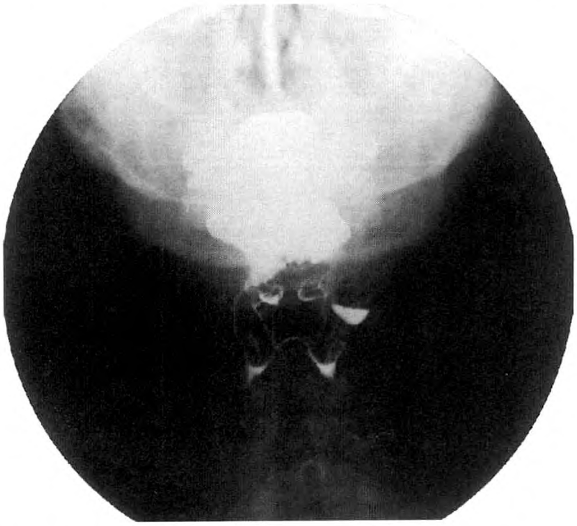


Fig 1. Contrast esophagogram. Anteroposterior view prior to stapling demonstrates left pharyngeal pouch.

From the Division of Otolaryngology, Duke University Medical Center, Durham, North Carolina.
CORRESPONDENCE — Patti C. Huang, MD, Box 3805, Division of Otolaryngology, Duke University Medical Center, Durham, NC 27710.

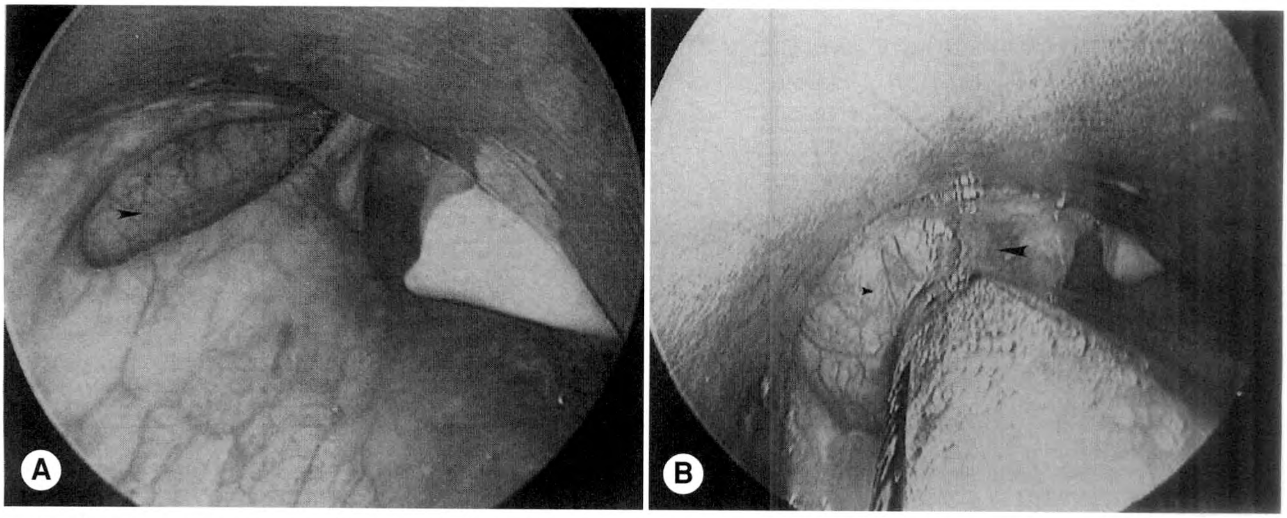


Fig 2. Endoscopic views. A) Pharynx and lateral pharyngeal pouch (arrowhead). B) With stapling device. Common wall (large arrowhead) between lateral pharyngeal pouch (small arrowhead) and pharynx is contained within blades of staple cartridge.

ynx was divided with the Endo-GIA 30 endoscopic stapler (US Surgical Corp, Norwalk, Conn).[3] Controlled by a trigger-activated device, the Endo-GIA 30 stapler allows simultaneous stapling and sectioning of tissue. The instrument has a distal replaceable cartridge that contains 3 rows of staples on each side of a midline retractable knife blade. The two anvils of the cartridge are placed around the tissue to be stapled and divided, and on activation of the trigger mechanism, the knife is advanced through the tissue at the same time the staples are placed. The shaft of the stapler has a diameter of approximately 12 mm and a length of 31.5 cm.

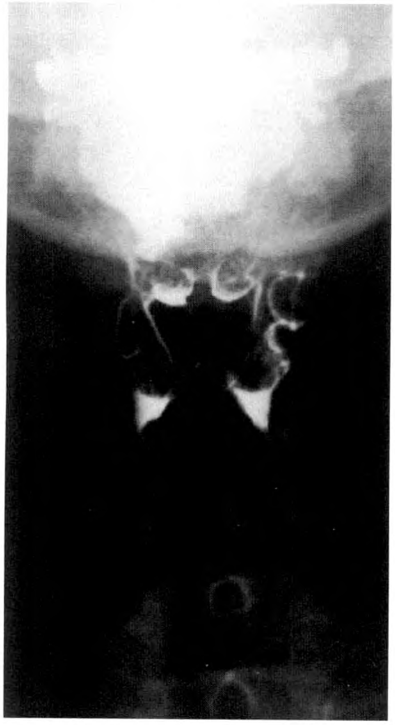


Fig 3. Contrast esophagogram. Anteroposterior view after stapling demonstrates emptying of contrast material into pharynx during swallowing, with no radiographic evidence of retained contrast in residual pouch.

The stapler was inserted into the pharyngeal pouch. It was then closed, with the common wall of the pouch and pharynx contained within the blades of the staple cartridge (Fig 2B). The position of the stapler was confirmed at all times by videoendoscopic monitoring. The endostapler was then activated, dividing and stapling the common wall.

The patient was observed in the hospital overnight after surgery. Intravenous fluids and antibiotics were continued during the hospitalization. Clear liquids were given by mouth the morning following the surgery. In addition, the patient was also started on antireflux medication.

One month after the procedure, the patient continued to do well, with no further symptoms of dysphagia.

DISCUSSION

The lateral pharyngeal pouch remains an uncommon cause of dysphagia. Clinical manifestations may include regurgitation of undigested food, throat irritation, hoarseness, and worsening pulmonary symptoms.[4] However, many patients remain asymptomatic. Diagnosis is demonstrated with barium swallow study.

The etiology includes both congenital and acquired theories. The pouches and diverticula may represent remnants of the second, third, or fourth branchial clefts.[5,6] Other factors support an acquired development. Prolonged pressure on anatomic weak points in the pharyngeal wall contributes to formation.[7] The area between the middle and inferior constrictors represents a common location. Pharyngeal pouches and diverticula occur in glass blowers and trumpet players, as well as older patients.

Terminology of the entity includes pharyngeal "ear," pharyngeal pouch or protrusion, and "true" diverticulum.[8] True diverticula may be identified by retention of the barium bolus and the presence of an isthmus.

Historically, treatment has varied according to patient symptoms and anatomy. Many patients remain asymptomatic despite incidental pharyngeal findings. External diverticulectomy has been performed for a patient with a true lateral pharyngeal diverticulum.[4]

Endoscopic stapling represents a new technique for treatment of the symptomatic lateral pharyngeal pouch. Division of the common wall forms a wide-mouthed communication between the pouch and the pharynx. A postprocedure barium swallow study reveals rapid emptying of contrast material into the pharynx during swallowing, with no radiographic evidence of retained contrast in a residual pouch (Fig 3).

SUMMARY

A patient with dysphagia including symptoms of regurgitation of food and worsening pulmonary symptoms was found to have a lateral pharyngeal pouch. The diagnosis was made by barium swallow study and confirmed by endoscopy. The characteristic barium swallow findings include retention of barium in a sac or diverticulum. Endoscopy showed a pouch in the left lateral pharynx, adjacent to the vallecula. Surgical therapy consisting of endoscopic stapling of the mucosal band separating the pouch from the pharynx was performed successfully, and the patient improved dramatically.

REFERENCES

1. Curtis DJ, Cruess DF, Crain M, Sivit C, Winters C, Dachman AH. Lateral pharyngeal outpouchings: a comparison of dysphagic and asymptomatic patients. Dysphagia 1988;2:156-61.
2. Dohlman G, Mattsson O. The endoscopic operation for hypopharyngeal diverticula. Arch Otolaryngol 1960;71:744-52.
3. Scher RL, Richtsmeier WJ. Endoscopic staple-assisted esophagodiverticulostomy for Zenker's diverticulum. Laryngoscope 1996;106:951-6.
4. Schwartz EE, Tucker JA, Holt GP. Cervical dysphagia: pharyngeal protrusions and achalasia. Clin Radiol 1981;32:643-50.
5. Clay B. Congenital lateral pharyngeal diverticulum. Br J Radiol 1972;45:863-5.
6. Wilson CP. Pharyngeal diverticula, their cause and treatment. J Laryngol Otol 1962;76:151-80.
7. Ettman IK, Ramey DR. Lateral pharyngeal diverticulum: unusual cause of dysphagia and hoarseness. Am J Gastroenterol 1967;47:490-7.
8. Bachman AL, Seaman WB, Macken KL. Lateral pharyngeal diverticula. Radiology 1968;91:774-82.

Ann Otol Rhinol Laryngol 108:1999

CLINICOPATHOLOGICAL CONSULTATION

SINONASAL MALIGNANT LYMPHOMAS: A DISTINCT CLINICOPATHOLOGICAL CATEGORY

RACHEL W. VIDAL, MD
ANN ARBOR, MICHIGAN

KENNETH DEVANEY, MD
ANN ARBOR, MICHIGAN

ALFIO FERLITO, MD
UDINE, ITALY

ALESSANDRA RINALDO, MD
UDINE, ITALY

ANTONINO CARBONE, MD
AVIANO, ITALY

Sinonasal lymphomas represent a distinct subset of extranodal head and neck lymphomas. While sinonasal lymphomas are relatively rare in Western countries, in Asian populations they are the second most frequent group of extranodal lymphomas, after gastrointestinal lymphomas. With advances in immunohistochemistry, these lymphomas have been separated into B-cell, T-cell, and most recently into natural killer (NK) cell phenotypes. The B-cell phenotype is typically located in the paranasal sinuses and has a slight predominance in Western countries. The T/NK-cell phenotype is the most common in Asian and South American countries. These tumors are typically located in the nasal cavity and have an aggressive, angioinvasive growth pattern that often results in necrosis and bony erosion. Thus, sinonasal lymphomas have been included in the past with other destructive malignant and benign lesions under the descriptive and nonspecific name lethal midline granuloma. Patients are classically in the sixth to eighth decades, with a 2:1 male-to-female ratio. The prognosis is generally better than that of nodal-based lymphomas of similar histologic grade. Treatment is a combination of local irradiation and chemotherapy with an anthracycline-based regimen.

INTRODUCTION

Malignant lymphomas arising in the nasal cavity and paranasal sinuses are relatively uncommon. Although lymphomas may be the most common nonepithelial malignant tumors of the nose, an obstructive mass in this location is far more likely to be a carcinoma than a lymphoma. It is this rarity that may cause clinicians to dismiss them as a benign inflammatory infiltrate. They are especially infrequent in Western populations, where they account for only 1.5% of all non-Hodgkin's lymphomas and 2.2% of extranodal lymphomas.[1] They constitute 5.8% to 8% of the extranodal lymphomas arising in the head and neck area.[2,3] In Asian countries, the incidence is significantly higher; there, they account for 2.6% to 6.7% of all lymphomas, and are the second most frequent group of extranodal lymphomas, after gastrointestinal lymphomas.[4,5]

SINONASAL LYMPHOMA: PHENOTYPE AND GEOGRAPHICAL DIFFERENCES

With advances in immunohistochemistry, a significant proportion of these lymphomas were found to be T-cell phenotypes. This is especially true in Asian populations, in which greater than 90% of sinonasal lymphomas are T-cell.[1,4-8] This high incidence of T-cell phenotypes has been found to be unrelated to infection with human T-cell leukemia virus (HTLV-1).[9-11] There is also a strong predominance of T-cell lymphomas in Peru and Guatemala. Studies have shown that 78% of sinonasal lymphomas in Peru and 88% in Guatemala are T-cell phenotype.[9,12] In the Guatemalan study, most of the patients were of Mayan descent. This finding is interesting, since the Mayans and Incas (from Peru) are believed to be descendants of Asian people who migrated across the Bering Straits land bridge during the Ice Age. Thus, the Asians, Peruvians, and Guatemalans may share a common genetic ancestry that makes them more predisposed to T-cell lymphomas.

More recently, further studies of Asian populations have found that many of the proliferating T-cell lymphocytes lack expression of several T-cell markers and possess an additional marker, CD56, suggesting a natural killer (NK) cell origin. These had been classified as T/NK cell lymphomas, having shared phenotypic features of both T and NK cells. More advances in immunophenotyping and molecular diag-

---

From the Department of Pathology, University of Michigan, Ann Arbor, Michigan (Vidal, Devaney), and the Department of Otolaryngology–Head and Neck Surgery, University of Udine, Udine (Ferlito, Rinaldo), and the Division of Pathology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano (Carbone), Italy.

CORRESPONDENCE — Alfio Ferlito, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Udine, Policlinico Città di Udine, Viale Venezia 410, 33100 Udine, Italy.

nostic studies have enabled better separation into T-cell and NK-cell lymphomas. However, clinically and histologically, the two groups share many similarities.[13]

In Western countries, B-cell lymphomas seem to predominate, reportedly constituting 55% to 85% of the sinonasal lymphomas.[12] The difference in incidence of B- and T-cell type lymphomas between Western and Asian populations has prompted some researchers to speculate whether the increased B-cell phenotype seen in Western populations is due to differences in inclusion criteria or due to true geographic differences. Some older studies excluded lesions that were classified as "polymorphic reticulosis" because they were thought to be malignant histiocytosis or benign inflammatory lesions, when in reality, most can be classified as T-cell lymphomas. Other studies consisted only of tumors from the paranasal sinuses, typically of the B-cell phenotype. By contrast, many Asian studies were restricted to tumors only involving the nasal cavity, which are more often of the T-cell phenotype.[6,14] Subsequent studies, primarily in Europe, have continued to show a slight B-cell predominance, but with a T:B cell ratio significantly higher than that seen in nodal-based lymphomas.[2]

EARLY NOMENCLATURE USED FOR SINONASAL LYMPHOMAS

"Lethal midline granuloma" is a *clinical* diagnosis used to describe a lesion that causes destruction of the nasal septum. Over the years, there has been confusion over the various terms used to refer to this *clinical condition*, names such as lethal granulomatous ulceration, rhinitis gangrenosa progressiva, and midline malignant reticulosis. Really, these describe a nonspecific clinical entity characterized by progressive, unrelenting ulceration and necrosis of the nasal cavity and the midfacial tissues.[4,15,16] Such a destructive lesion can be produced by a variety of diseases, including infections (such as syphilis, tuberculosis, leprosy), collagen vascular or autoimmune diseases, *sinonasal lymphomas*, and other malignant tumors.[8,17]

One of the most common benign causes of lethal midline granuloma is a collagen vascular disease, Wegener's granulomatosis.[15] It is thus a misleading term, since many cases are not lethal and they are not always midline.

Eichel et al[18] and others[1,3,4] coined the term polymorphous reticulosis to describe cases that were initially diagnosed as malignant lymphoma but that were found to have a polymorphic cellular composition. The cases of "polymorphous reticulosis" described in the literature have been found to be T-cell lesions.

Another equally confusing term is angiocentric immunoproliferative lesion (AIL), which was proposed by Lipford et al[19] to describe a spectrum of disorders ranging from benign vasculitis to lymphomatoid granulomatosis to angiocentric lymphoma. All of these entities are characterized by angiocentric, polymorphic lymphoreticular infiltrates.[20] The lesions are typically found in the skin, lungs, or upper respiratory tract. While angiocentric lymphomas of the sinonasal area are of the T-cell phenotype, most of the angiocentric lesions in the lung are of the B-cell phenotype.[21]

In conclusion, from a clinical point of view, it may still be useful to retain descriptive or classic clinical terms.[22] However, this historical nomenclature is potentially dangerous when used without a precise characterization of the underlying lymphoproliferative disorders.[23]

T/NK CELL LYMPHOMAS

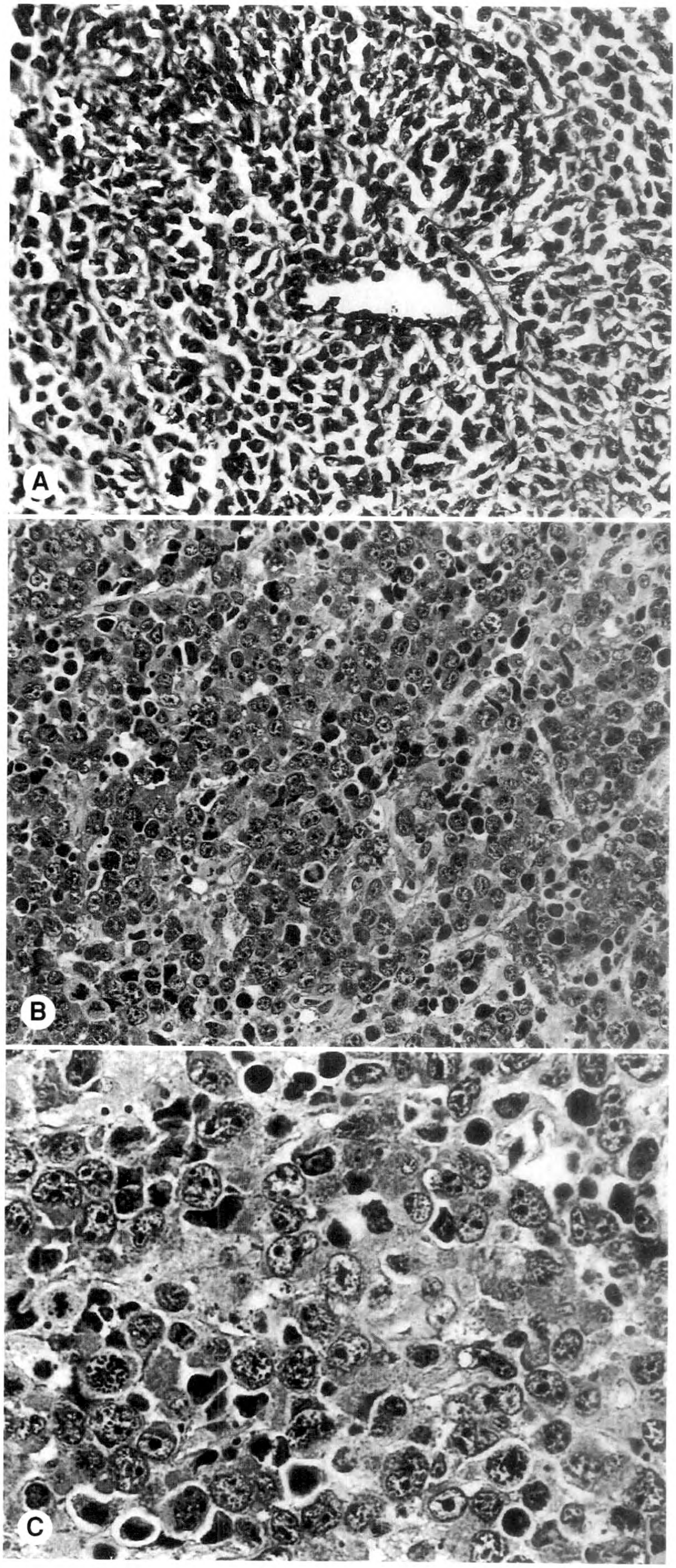
As mentioned in the Introduction, there has been an evolution in the understanding of T-cell lymphomas resulting in, first, the combined classification of T/NK cell and, later, further separation of these tumors into T-cell and NK cell phenotypes.

The T/NK cell lymphomas have unique features that help to distinguish them from B-cell lymphomas. They are characterized by progressive, unrelenting ulceration and necrosis not seen in B-cell lesions. There is often severe destruction of the nasal septum and facial midline structures, which has won them names such as lethal midline granuloma or rhinitis gangrenosa progressiva.[21,24] They are frequently associated with angioinvasion, coagulative necrosis, and epitheliotropism (see Figure, A).

The majority of cases are now classified as nasal T-cell lymphoma/angiocentric lymphoma according to the Revised European-American Lymphoma (REAL) classification, but were previously known as polymorphous reticulosis.[20,25] As the name implies, these tumors are composed of a polymorphous infiltrate of benign inflammatory cells, eosinophils, neutrophils, histiocytes, and benign lymphocytes mixed with atypical, malignant cells. They are characterized by angiocentricity or angiotropism in which tumor cells infiltrate and destroy blood vessel walls.[1,8,14] This results in a variable degree of geographic necrosis in most cases. In contrast, B-cell lymphoma cells tend to surround and compress, not invade, blood vessels; thus, necrosis is extremely rare.

Peripheral T-cell lymphomas are characterized by

Sinonasal malignant lymphomas (H & E). A) T-cell lymphoma, characterized by angioinvasion and angionecrosis. B) Diffuse large cell B-cell lymphoma. C) Large cell B-cell lymphoma, characterized by large cells with vesicular chromatin and conspicuous nucleoli.



a mixture of small, medium, and large atypical lymphoid cells. Depending on the relative proportion of each cell type, they are classified as small cleaved, mixed-cell, or large cell types.

The small cells have elongated, angulated nuclei, dense chromatin, and scanty cytoplasm and are difficult to distinguish from small cleaved, follicular-center B-cells.

The medium-sized and large cells have round to highly convoluted nuclei, vesicular or coarsely stippled chromatin with a moderate amount of pale cytoplasm, and 1 or more distinct nucleoli. It has been suggested that the cytoplasmic pallor and associated vascular proliferation provide a clue that one may be dealing with a peripheral T-cell lymphoma.[8]

Other patterns associated with the T/NK cell phenotype include anaplastic large cell lymphoma (Ki-1/CD30) and large cell immunoblastic lymphoma. The anaplastic large cell type is characterized by sheets of large cells with irregular, bizarre-shaped nuclei, including ringed and horseshoe shapes. The immunoblastic type has an appearance similar to that of its B-cell counterpart.

Immunophenotype. Immunohistochemical studies and flow cytometric analyses have demonstrated that many of the T/NK lymphomas have a peripheral T-cell phenotype. They express common T-cell markers such as CD2, CD3, and CD5. CD7, another T-cell marker found on normal mature, circulating T-cells, is frequently lost in the malignant transformation and may not be expressed. Any of the cell markers can be lost; CD7 is merely the most common. These cells also lack TdT, CD34, and CD1a, which are markers of immature, thymic T-cells. They also lack B-cell markers such as CD20.

However, an increasing number of cases are found to have an NK cell phenotype, up to 65%.[18] The NK cell lymphomas are a distinct group of tumors composed of cells with an unusual immunophenotype. These cells are positive for some T-cell antigens such as CD2, CD43, and CD45RO, but lack other T-cell antigens such as CD3, CD4, CD5, and CD7. The absence of these antigens is more than just the aberrant loss of markers seen in other malignant T-cell lymphomas. Most important, these tumors cells also possess CD56, a marker of NK cells.[13,21,26-28]

Both T-cells and NK cells are derived from the same progenitor cell, which is capable of differentiation into either a T-cell or an NK cell.[28] Thus, NK cells may express some T-cell markers, including CD2, CD7, and CD8, but they characteristically lack CD5 and often CD3. Unlike mature peripheral NK cells, the malignant NK cells typically lack the other NK cell markers, CD16 and CD57.[20,21,27] In summary, the classic NK cell lymphoma cell expresses CD2 and CD56 positivity, lacks CD3, typically lacks CD16 and CD57, and has a low frequency of expression of other T-cell markers.

An important distinction between T-cells and NK cells is that NK cells do not exhibit rearrangements of the T-cell receptor (TCR) genes. T-cells have rearrangement in the β and γ TCR genes and loss of the δ genes, whereas NK cells have germline configurations of TCR β, γ, and δ genes or a complete absence of expression of the TCR.[27] Thus, by means of Southern blot techniques for gene rearrangement analyses and immunohistochemical stains, a distinction between the two cell types can be made.

So, if the two types share similar histologic features and even common T-cell antigen markers, are there any significant differences between them? Studies of CD56-positive NK cell lymphomas, not only in the sinonasal region but also in other areas such as skin and lung, demonstrate that the tumors have a very aggressive behavior with more extensive angioinvasion than T-cell lymphomas. Some have suggested that since CD56 is a cell adhesion molecule (N-CAM), its expression on malignant cells may mediate cellular adhesion to blood vessels, resulting in more pronounced angiocentric and angiodestructive infiltrates. Patients with NK lymphomas are also more likely to have fevers and skin rashes.[27,29]

Association With Epstein-Barr Virus. Numerous studies have demonstrated that both T-cell and NK cell lymphomas of the sinonasal region have a high incidence of Epstein-Barr virus (EBV) infection.[6,9,11,12,20,30] There is a preponderance of EBV-associated T/NK-cell lymphomas in Asian and South American countries. All but 1 of the Guatemalan patients with the T/NK-cell phenotype studied by van de Rijn et al[12] were positive for EBV by in situ hybridization, and all the sinonasal T-cell lymphomas studied in Peru were positive for the virus.[9]

Although the frequency of sinonasal T/NK-cell lymphomas is lower in Western countries, the association of EBV and these lymphomas parallels that of Asian and South American countries.[11,20,31] It appears that regardless of their geographic location, there is a strong association between them. However, it has been suggested that sinonasal T/NK-cell lymphomas are seen more often in less developed countries, where EBV infections occur at an earlier age.[9]

It is unclear what role the virus plays in the development of sinonasal lymphomas. It is known that NK cells are relatively uncommon in normal nasal mucosa, representing less than 2% of lymphocytes.[2,32] Natural killer cells provide resistance to and protection against viral infections, since they are capable of mediating cytotoxicity without major histocompatibility restriction or prior sensitization.[33] It is believed that in the presence of EBV, the NK cells become activated and are recruited to the sinonasal area. It is possible that once stimulated, a single cell or group of cells continues to proliferate, resulting in a clonal population. This same EBV-induced stimulation is believed to be the cause of posttransplant immunoproliferative disorders.

T/NK-cell lymphomas of the sinonasal region are, almost without exception, EBV-associated. However, the relationship between EBV and T/NK-cell lymphomas from other sites is much weaker. The virus has been detected in fewer than 1% of cutaneous lymphomas, in 13% to 36% of gastrointestinal tract lymphomas, and in 18% of nodal T-cell lymphomas.[34]

B-CELL LYMPHOMAS

Outside of the original lymphoid tissues of Waldeyer's ring, there is a mixed population of lymphocytes that resides in the subepithelial areas of the nasal cavity. A smaller population of lymphocytes is scattered among submucosal glands and within deep vascular stroma. More than half of these lymphocytes, especially those forming aggregate clusters, are B-cells. It is believed that extranodal B-cell non-Hodgkin's lymphomas derive from these cells.[35]

Follicular lymphomas in the sinonasal region are rare. In the majority of studies, all of the sinonasal lymphomas demonstrated a diffuse growth pattern.[2,7,8,10,21,28,32,36] However, there were a few exceptions, such as in the Abbondanzo and Wenig[6] study, in which 6 of 120 cases of sinonasal lymphoma showed a follicular pattern, the majority of which were composed of large cells. Unlike T-cell lymphomas, angiocentricity and geographic necrosis are rarely seen in B-cell lesions.

A review of the literature, including several large studies, concludes that most sinonasal B-cell lymphomas are intermediate-grade. The classifications were based on either the Working Formulation or the Kiel Classification. The most common types reported are diffuse large cell and diffuse mixed small cleaved and large cell.[6,7,37]

The diffuse large cell type is characterized by sheets of large cleaved and/or noncleaved cells and a minor population (<50%) of small cleaved cells (see Figure, B). The large cells have a vesicular chromatin and a conspicuous solitary nucleolus or multiple small nucleoli located at the nuclear membrane (see Figure, C). The mixed small cleaved and large cell type consists of an admixture of these large cells and small cells with scant cytoplasm and cleaved or angulated nuclei.

Other histologic patterns commonly seen include diffuse small cleaved cell lymphoma, immunoblastic lymphoma, diffuse small noncleaved cell (Burkitt-like) lymphoma, and small lymphocytic lymphomas.

Diffuse small cleaved cell lymphoma is composed predominantly of small lymphocytes with prominent nuclear folds and clefts with coarse, condensed chromatin and inconspicuous nucleoli and with scanty cytoplasm. Scattered among them are rare large cells.

Immunoblastic lymphoma is characterized by round or oval cells with large central nucleoli and abundant basophilic cytoplasm. Nuclei may appear angular or crescent and are displaced peripherally by a prominent perinuclear hof. Frequently, there are numerous mitoses. Immunohistochemical stains show a light or heavy chain restriction. It is important to distinguish this tumor type from other types of large cell lymphoma, because these patients have significantly shorter survival.

Diffuse small noncleaved cell (Burkitt-like) lymphoma has a starry sky pattern due to a high mitotic rate. Like immunoblastic lymphoma, this is a high-grade lesion with an aggressive course. It is more commonly seen in the pediatric age group.

Small lymphocytic lymphomas are a homogeneous population of small, noncleaved cells with scant cytoplasm and interspersed, patchy areas of larger paraimmunoblastic cells forming proliferation centers. Much less frequently reported are plasmacytomas and immunocytomas (Waldenström's).

Immunophenotype. Immunohistochemical stains of these tumors are positive for the B-cell markers CD20 (L26) and CD79a (a newly identified antigen seen on a wider spectrum of B-cells, including more immature B-cells). They are negative for the T-cell markers CD3, CD45RO (A6), and CD43 (Leu22). However, coexpression of CD20 and CD43 may be seen in some cases of B-cell lymphoma.

CLINICAL FEATURES OF SINONASAL LYMPHOMAS

Sex. Independent of the phenotype, there is a male predominance, with an average male-to-female ratio of 2:1.

Age. T-cell lymphomas typically involve a younger age group than the B-cell phenotype, with a median age of 52 years. There have been suggestions of an

COMMON PRESENTING CLINICAL SYMPTOMS OF SINONASAL MALIGNANT LYMPHOMA
Nasal obstruction
Unilateral facial, cheek, and nasal swelling
Diplopia or blurred vision
Nasal or cheek pain
Epistaxis
Headache
Nasal discharge or repeated infection
Unilateral proptosis
Cranial nerve paralysis

even greater male predilection for the NK cell phenotype, and an even younger median age of 50 years.

Although they are typically seen in adults in their fourth and fifth decades, sinonasal lymphomas are also seen in young children, with a median age of 5 years. Sinonasal involvement in children is actually not surprising, given that there is a higher incidence of extranodal lymphomas in children than in adults. In one large study at Sloan-Kettering, 16.4% of pediatric extranodal lymphomas had a primary site of involvement in the nasal or paranasal sinuses or oropharyngeal cavity.[38]

Site of Primary Involvement. Most sinonasal lymphomas are stage I or II lesions at initial presentation. However, they are typically bulky tumors with local, infiltrative growth resulting in prominent bony erosion (of the sinus walls).[27,39] The most frequent sites of disease in Western countries are the maxillary antrum, nasal cavity, and ethmoid sinuses. In Asian countries, the nasal cavity is more commonly involved than the paranasal sinuses.[7] This site predilection is due to the prevalence of T-cell lymphomas, which are frequently located in the nasal cavity and the hard or soft palate.[6,13,14]

In the majority of cases, multiple sinuses are initially affected.[6,35] Most frequently, the tumors, B- or T-cell phenotypes, involve 1 or more nasal cavities. Involvement of 1 or more paranasal sinuses is more typical of B-cell types, whereas involvement of the nasal cavity is more typical of T-cell types. Less commonly, the lymphomas, generally of a T-cell phenotype, will invade adjacent sites such as the hard palate, cheek, and orbit.[6]

Most of the lymphomas in the nasal cavity are located in the subepithelial areas. Few are located in the epithelium or within deep vascular stroma. As with other extranodal lymphomas, dissemination to distant sites is infrequent and is typically to other extranodal locations, such as the gastrointestinal tract, breast, liver, kidney, larynx, testis, and prostate. T-cell lymphomas have a tendency to disseminate to skin.[2]

Clinical Symptoms. The most common presenting symptoms are nasal obstruction and unilateral facial, cheek, or nasal swelling.[32,35] Other, less frequent symptoms include diplopia or blurred vision, headache, epistaxis, and nasal or cheek pain (see Table). Occasionally, patients will present with nasal congestion and discharge, occasionally purulent. As a general rule, low-grade lesions present as masses with associated obstructive symptoms. High-grade lesions and T-cell lesions are more likely to be associated with nonhealing ulcers, cranial nerve manifestations, and other aggressive features.[6] Some patients have a history of chronic sinusitis or rhinitis or allergies.[35] Many patients have even had previous treatment, including surgical intervention, for their symptoms. Systemic symptoms are rare. The symptoms are typically present from 1 month to a year prior to diagnosis, most commonly 8 weeks or less.[32] In young children, the most common initial symptoms are neck swelling and sore throat. In contrast to adults, many pediatric patients present with complaints of difficulty breathing or mouth breathing.

Radiology. Bony erosion is a predominant feature. High-grade B-cell tumors have been noted to cause orbital soft tissue and osseous destruction, whereas nasal septal perforation or destruction is more associated with high-grade T-cell lesions.[6]

A definite mass, or less often, cloudy or opaque sinuses are apparent on radiographs.[35] Computed tomography scans are particularly helpful in evaluating the extent of destruction and involvement of sinuses and orbits.

Gross Description. In many cases of T/NK cell lymphomas, there is invasion of the epithelial structures, with extensive ulceration and superficial necrosis. B-cell lymphomas rarely cause necrosis or ulceration, so these lesions would likely have an intact, unremarkable-appearing overlying mucosa. The tumors themselves are generally described as gray, white, or tan friable tissue fragments.

PROGNOSIS AND TREATMENT

Lymphomas of the sinonasal region generally have a better prognosis than nodal lymphomas of similar histologic grades. According to a 1996 study of 70 patients with lymphoma of the nasal cavity and paranasal sinuses, the 5-year overall survival for all the types (B, T, NK) is 52%, and the 5-year freedom from progression (FFP) is 57%.[7] Superior overall survival was found in patients of a younger age, with early stage of disease, with an absence of B-symptoms, with a lower lactate dehydrogenase level, and in those receiving an anthracycline-based chemotherapy such as doxorubicin.[37] However, the only factors independently related to overall survival are the stage of disease and patient age.[7]

Sinonasal lymphomas typically present with low stages (stage IE or IIE), a likely factor contributing to their better prognosis. Patients with higher-stage disease (IIIE or IVE) tend to have a higher risk of relapse and a poor response to treatment.

Surprisingly, multiple studies have concluded that tumor immunophenotype (B or T/NK cell) is *not* an independent prognostic factor.[7,12,37] T-cell lymphomas tend to present with more advanced disease and the presence of B-symptoms, features associated with poorer prognosis. They are considered more aggressive, with greater tissue invasion and bony erosion. Univariate analyses demonstrate that T-cell lymphomas are indeed associated with a lower cure rate, a higher relapse rate, and worse overall survival. However, multivariate analyses conclude that as an *independent* factor, phenotype does not affect prognosis.[37]

The most important finding of recent studies has been that the addition of chemotherapy significantly improved the 5-year FFP for all stages of disease, especially stage IIE.[9,37,40] In the past, these lymphomas were treated with local radiotherapy with a good response, often with complete tumor regression. However, there is a high incidence of distant and local recurrence. In one study, 49% of patients treated with local irradiation alone had a recurrence.[40] With a combination treatment of chemotherapy, especially an anthracycline-based regimen (ie, CHOP), and local radiotherapy, there is a reduction in recurrence and metastasis, resulting in an overall improved survival. Patients treated with chemotherapy alone have a higher risk of local recurrence.[7,21,34,37]

For patients with low-stage tumors (stage IE:T1-3) in whom chemotherapy may be contraindicated, radiotherapy alone is felt to be adequate. However, given the high risk of distant recurrence, irradiation alone would not be sufficient treatment in patients with higher-stage disease. Also, as in the case of other lymphomas, surgical resection is not considered an appropriate therapy for sinonasal lymphomas.[32]

For cases refractory to the combined treatment, bone marrow transplant has been considered and even attempted in a few cases, with equivocal results. Liang et al[34] reported on 2 patients who received autologous bone marrow transplants. One patient had a clinical remission of greater than 2 years, but the other died following disease relapse to his bone marrow only 4 months after transplant. Another report showed improved survival for 2 patients with NK lymphomas treated with autologous transplants.[28]

Despite treatment with combined chemotherapy and radiotherapy, there is still a concern over local failures, more prevalent in T-cell phenotypes, and central nervous system (CNS) relapses. Patients most at risk for CNS involvement have intermediate- or high-grade tumors in the anatomic vicinity of the maxillary sinus (above the pterygopalatine line).[7,40] Current recommendations are for irradiation to the CNS only in patients with documented CNS disease, and not as a prophylactic measure. To rule out CNS involvement, a lumbar puncture and magnetic resonance imaging of the brain are recommended for patients with tumor involving the skull base region.[40]

APPROACH TO BIOPSY

Morphologically, sinonasal lymphomas can be difficult to distinguish from destructive non-neoplastic processes or other malignant neoplasms. Radiographically, these tumors mimic carcinomas, especially squamous cell carcinomas, which are far more prevalent in both Western and Asian populations than lymphomas. Even the gross appearance may be that of a carcinoma. Therefore, the surgeon is likely to have a low suspicion of lymphoma. The biopsy specimens are thus removed and immediately placed in formalin. However, the best approach would be to submit the specimen fresh and unfixed to the pathologist for a lymphoma workup.

The lymphoma evaluation includes several important steps not otherwise performed for tumors. A portion of the fresh tissue is frozen for possible future molecular diagnostic studies should they be deemed necessary for diagnosis. A small portion of the fresh tissue is minced and made into a cell suspension that can be used for flow cytometric analysis or frozen for future analysis. Several "touch prep" slides are made on which fresh tissue is lightly touched to a glass slide to provide individual cells that can later be stained with special stains that cannot be performed on formalin-fixed, processed tissues.

The most important step in the lymphoma processing is for a large portion of the specimen to be fixed in B-5, a mercury-based fixative, which enhances the nuclear detail and allows for better evaluation and differentiation of lymphocytes. The remaining tissue is then placed in standard formalin fixative.

The process, although elaborate, provides for all components necessary to diagnose and classify a lymphoma. Of course, a diagnosis of carcinoma or sarcoma can be made on either the formalin- or B-5–fixed tissue.

Another, equally important point is that unlike carcinomas that arise in a dysplastic epithelium, lymphomas are subepithelial. They may be masked by an overlying non-neoplastic, pleomorphic infiltrate or, as in the case of many T/NK cell types, by large areas of necrosis.[13] Thus, a superficial sampling of a radiographically suspicious area may be negative despite the presence of a deeper underlying malignant lymphoma. Also, angiocentricity and angioinvasion, features important for the diagnosis, often require deeper biopsies.[2,13] Last, it is often difficult to differentiate between the neoplastic and reactive cells on frozen sections, especially in cases in which there is a predominance of neoplastic small cells; therefore, in most cases the diagnosis must be deferred to permanent sections.

REFERENCES

1. Fellbaum C, Hansmann ML, Lennert K. Malignant lymphomas of the nasal cavity and paranasal sinuses. Virchows Arch [A] Pathol Anat Histopathol 1989;414:399-405.

2. Campo E, Cardesa MD, Alos L, et al. Non-Hodgkin's lymphomas of nasal cavity and paranasal sinuses. Am J Clin Pathol 1991;96:184-90.

3. Wong DS, Fuller LM, Butler JJ, Shullenberger CC. Extranodal non-Hodgkin's lymphomas of the head and neck. Am J Roentgenol Radium Ther Nucl Med 1975;123:471-81.

4. Ho F, Choy D, Loke SL, et al. Polymorphic reticulosis and conventional lymphomas of the nose and upper aerodigestive tract. Hum Pathol 1990;21:1041-50.

5. Ng CS, Chan J, Lo S, Poon YF. Immunophenotypic analysis of non-Hodgkin's lymphomas in Chinese. A study of 75 cases in Hong Kong. Pathology 1986;18:419-25.

6. Abbondanzo S, Wenig B. Non-Hodgkin's lymphoma of the sinonasal tract. Cancer 1995;75:1281-91.

7. Logsdon M, Ha C, Kavadi V, Cabanillas F, Hess M, Cox J. Lymphoma of the nasal cavity and paranasal sinuses. Cancer 1997;80:477-88.

8. Chan J, Ng CS, Lau WH, Stephen TH. Most nasal/nasopharyngeal lymphomas are peripheral T-cell neoplasms. Am J Surg Pathol 1987;11:418-29.

9. Arber DA, Weiss LM, Albujar PF, Chen YY, Jaffe E. Nasal lymphomas in Peru. High incidence of T-cell immunophenotype and Epstein-Barr virus infection. Am J Surg Pathol 1993;17:392-9.

10. Wilder WH, Harner SG, Banks PM. Lymphoma of the nose and paranasal sinuses. Arch Otolaryngol 1983;109:310-2.

11. De Bruin PC, Jiwa M, Oudejans JJ, et al. Presence of Epstein-Barr virus in extranodal T-cell lymphomas: differences in relation to site. Blood 1994;83:1612-8.

12. van de Rijn M, Bhargava V, Molina-Kirsch H, et al. Extranodal head and neck lymphomas in Guatemala: high frequency of Epstein-Barr virus–associated sinonasal lymphomas. Hum Pathol 1997;28:834-9.

13. Petrella T, Delfau-Larue MH, Caillot D, et al. Nasopharyngeal lymphomas: Further evidence for a natural killer origin. Hum Pathol 1996;27:827-33.

14. Ferry J, Sklar J, Zukerberg L, Harris N. Nasal lymphoma. Am J Surg Pathol 1991;15:268-79.

15. Ishii Y, Yamanaka N, Ogawa K, et al. Nasal T-cell lymphoma as a type of so called "lethal midline granuloma." Cancer 1982;50:2336-44.

16. Gaulard P, Henni T, Marolleau J, et al. Lethal midline granuloma (polymorphic reticulosis) and lymphomatoid granulomatosis. Cancer 1988;62:705-10.

17. Tsokos M, Fauci AS, Costa J. Idiopathic midline destructive disease (IMDD). A subgroup of patients with the "midline granuloma" syndrome. Am J Clin Pathol 1982;77:162-8.

18. Eichel BS, Harrison EG Jr, Devine KD, Scanlon PW, Brown HA. Primary lymphoma of the nose including a relationship to lethal midline granuloma. Am J Surg Pathol 1966;112:597-605.

19. Lipford EH, Margolick JB, Longo DL, Fauci AS, Jaffe ES. Angiocentric immunoproliferative lesions: a clinicopathologic spectrum of post-thymic T-cell proliferations. Blood 1988;72:1674-81.

20. Kanavaros P, Lescs MC, Briere J, et al. Nasal T-cell lymphoma: a clinicopathologic entity associated with peculiar phenotype and with Epstein-Barr virus. Blood 1993;81:2688-95.

21. Van Gorp J, De Bruin PC, Sie-Go DMDS, et al. Nasal T-cell lymphoma: a clinicopathological and immunophenotypic analysis of 13 cases. Histopathology 1995;27:139-48.

22. Friedmann I. Ulcerative/necrotizing diseases of the nose and paranasal sinuses. Curr Diagn Pathol 1995;2:236-55.

23. Cleary KR, Batsakis JG. Sinonasal lymphomas. Ann Otol Rhinol Laryngol 1994;103:911-4.

24. Salhany KE, Pietra G. Extranodal lymphoid disorders. Am J Clin Pathol 1993;99:472-85.

25. Harris NF, Jaffe ES, Stern H, et al. A revised European-American Classification of Lymphoid Neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-92.

26. Wong KF, Chan JKC, Ng CS, Lee KC, Tsang WYW, Cheung MMC. CD56 (NKH1) positive hematolymphoid malignancies: an aggressive neoplasm featuring frequent cutaneous/mucosal involvement, cytoplasmic, azurophilic granules and angiocentricity. Hum Pathol 1992;23:798-804.

27. Alan KS, Chiang MB, Srivastava G, Lau PWF, Ho FCS. Differences in T-cell receptor gene rearrangement and transcription in nasal lymphomas of natural killer and T-cell types. Hum Pathol 1996;27:701-7.

28. Kwong Y, Chan A, Liang R, et al. CD56 sup + NK lymphomas: clinicopathological features and prognosis. Br J Haematol 1997;97:821-9.

29. Tsang WY, Chan J, Yip T, et al. In-situ localization of Epstein-Barr virus encoded RNA in non-nasal/nasopharyngeal CD56-positive and CD56-negative T-cell lymphomas. Hum Pathol 1994;25:758-65.

30. Harabuchi Y, Yamanaka N, Kataura A. Epstein Barr virus in nasal T-cell lymphoma in patients with lethal midline granuloma. Lancet 1990;335:128-30.

31. Weiss LM, Gaffey MJ, Chen Y-Y, Frierson HF. Frequency of Epstein-Barr viral DNA in "Western" sinonasal and Waldeyer's ring non-Hodgkin's lymphomas. Am J Surg Pathol 1992;16:156-62.

32. Frierson H, Mills S, Innes D. Non-Hodgkin's lymphomas of the sinonasal region: histologic subtypes and their clinicopathologic features. Am J Clin Pathol 1984;81:721-7.

33. Weiss LM, Arber DA, Strickler JG. Nasal T-cell lymphoma. Ann Oncol 1994;5(suppl 1):539-42.

34. Liang R, Todd D, Chan TK, et al. Treatment outcome and prognostic factors for primary nasal lymphoma. J Clin Oncol 1995;13:666-70.

35. Frierson H, Innes D, Mills S, Wick M. Immunophenotypic analysis of sinonasal non-Hodgkin's lymphomas. Hum Pathol 1989;20:636-42.

36. Liang R, Todd D, Chan TK, et al. Nasal lymphomas: a retrospective analysis of 60 cases. Cancer 1990;66:2205-9.

37. Liang R, Todd D, Ho F. Aggressive non-Hodgkin's lymphoma: T-cell versus B-cell. Hematol Oncol 1996;14:1-6.

38. Wollner N, Mandell L, Filippa D, Exelby P, McGowan N, Lieberman P. Primary nasal-paranasal oropharyngeal lymphomas in the pediatric age group. Cancer 1990;65:1438-44.

39. Graper RG, Orenstein HH, Rohrich RJ, Byrd RJ, Rich BK. Idiopathic midline granuloma — current classification and management controversies. Ann Plast Surg 1996;37:532-7.

40. Burton GV, Atwater S, Borowitz MJ, Huang AT. Extranodal head and neck lymphoma: prognosis and patterns of recurrence. Arch Otolaryngol Head Neck Surg 1990;116:69-73.

≈

FUNCTIONAL ENDOSCOPIC SINUS SURGERY

Functional Endoscopic Sinus Surgery — Basic and Advanced Techniques will be held in Graz, Austria, in English (July 1-3, 1999) and in German (September 2-4, 1999). For more information, contact Claire Zwerina, Secretary to Prof Stammberger, ENT-Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43/316/385/3425.

ACKNOWLEDGMENT OF REVIEWERS

Peer review is a process aimed at ensuring high-quality professional publications. The extent to which that goal is achieved depends on the willingness of a body of reviewers to share their time, experience, and abilities to assist in evaluating materials submitted for publication. It is with a great deal of gratitude that we acknowledge the persons listed below for serving the ANNALS as reviewers from December 1, 1996, through December 31, 1998. Their participation has contributed importantly to the growth and distinction of this journal.

Brian F. McCabe, MD
Editor

Paul J. Abbas
Michael I. Abecassis
Allan Abramson
Monzer Abu-Yousef
Harold Adams
Stephen Albedelda
Cuneyt Alper
Ramsey Alsarraf
Fariborz Alipour
J. H. J. Allum
Al Aly
Clarence Angelborg
Michael A. Apicella
Wolfgang Arnold
James P. Aubuchon
Armelle Baeza-Sqiban
Daniel Bagger-Sjöbäck
Lauren Bakaletz
Zuhair Ballas
Robert W. Baloh
Stephen Bansberg
Hugh O. Barber
Julie M. Barkmeier
John G. Batsakis
Nancy M. Bauman
James D. Baxter
Bradley Bechtelsbauer
Bruce B. Becker
William Becker
Douglas M. Behrendt
William Bell
Bruce Benjamin
Kevin S. Berbaum
LaVonne Bergstrom
Joel M. Bernstein
Robert A. Bertrand
David Beste
Hugh F. Biller
Warren P. Bishop
Stanley Blaugrund
Andrew Blitzer
Thomas F. Boat
Andreas Bohmer
Derald E. Brackmann
James H. Brandenburg
Paul Bretlau
Kathryn E. Bright
Mitchell F. Brin
Bradley E. Britigan
Itzhak Brook
Bruce E. Brown
Carolyn J. Brown
William E. Brownell
Richard A. Buckingham
John E. Buenting
Robert Bumstead
Brian B. Burkey
Thomas C. Calcaterra
Kathleen Campbell
John W. Canady
Ming Y. Cao
Thomas E. Carey
Ricardo Carrau
Keith D. Carter
Donald M. Caspary
Janina K. Casper
Nicholas J. Cassissi
Nikolajs Cauna
J. Ryan Chandler
B. Charlton
Richard A. Chole
James Chow
Patricia Chute
Graeme Clark
Heather Clark
Keith L. Clark
Randall A. Clary
Jack D. Clemis
Bernard Cohen
Joseph Cohen
Noel L. Cohen
Seymour R. Cohen
Newton J. Coker
Sharon Collins
Raymond H. Colton
Christopher Conley
George H. Connor
Donald S. Cooper
G. Cortopassi
Jorge B. Corvera
James Cotticia
Robin Cotton
Albert E. Cram
Margie Crawford
F. P. Cremers
Roger L. Crumley
William S. Crysdale
J. R. Cullen
Charles W. Cummings
James Cuyler
Christer Dahlin
Kathleen Daley
Larry Dalzell
Adrian Davis
R. K. Davis
Herbert H. Dedo
Hugh O. DeFries
James M. DelGaudio
Gianfranco Delprete
Thomas F. DeMaria
Marilyn Demorest
Craig S. Derkay
Robert A. Dobie
Joseph Dohar
David F. Dolan
Debra Don
Patrick J. Doyle
William J. Doyle
James A. Duncavage
Arndt J. Duvall
Ann M. Dvorak
Mark E. Dyken
John de Groot
Donald Eddington
David Edelstein
Jos J. Eggermont
Josef Elidan
Gregory Ellen
Adel K. El-Naggar
Ramon Esclamado
Martin Feldman
Alfio Ferlito
William Fiederspiel
Richard W. Fincham
Jonathan Finder
Eileen Finnegan
Ugo Fisch
E. W. Fisher
Peter J. Fitzgibbons
H. Fliesch
Robert Foote
Charles N. Ford
Karin Forsgren
Mary A. S. Frable
Sarah Frankel
J. Frederickson
R. W. Freeman
Marvin Fried
Ellen Friedman
Imre Friedmann
Gary K. Frykman
David W. Fulker
Gerry F. Funk
Joseph M. R. Furman
Neil Futran
Richard R. Gacek
Patrick Gannon
Bruce J. Gantz
Emilio Garcia-Ibanez
George A. Gates
Thomas V. Getchell
G. Scott Giebink
Michael E. Glasscock III
James Goeken
Helmuth Goepfert
W. J. Goodwin, Jr
Michael Gorga
Luisa Gorza
Marcos Goycoolea
Scott M. Graham
Steven D. Gray
Judith Grayhack
Aksel Grøntved
Charles Gross
Kenneth Grundfast
Aina J. Gulya
Bahman Guyuron
Joseph Haddad Jr
Mark Haggard
James W. Hall III
M. A. Hamid
Steven Handler
Douglas W. Hanto
Yasuo Harada
Paul Harari
Gady Har-El
Stephen G. Harner
Jeffrey P. Harris
Donald F. N. Harrison
Gregory Hartwig
Ilmo E. Hassinen
Bruce H. Haughey
William Hauser
Michael Hawke
Joseph E. Hawkins
Gerald B. Healy

Patricia Hebda
Mary J. C. Hendrix
Robert A. Hendrix
Bernard J. M. Hess
John Hewitt
Douglas Hicks
Ole Hilberg
Allen Hillel
Ronald Hinchcliffe
Michael Hinni
Minoru Hirano
Henry T. Hoffman
Raymond J. Hohl
Lauren D. Holinger
Andrew Hotaling
Jack V. Hough
Howard P. House
William F. House
Sharon Hravbosky
Gordon B. Hughes
Egbert H. Huizing
David Hurst
David H. Hussey
Makoto Igarashi
Henrich Iro
Glen Isaacson
Naoki Ishiguro
Nobuhiko Isshiki
J. Iwamoto
Robert K. Jackler
C. G. Jackson
Gary P. Jacobson
Bruce Jafek
Burton F. Jaffe
Robert A. Jahrsdoerfer
Ivo Janecka
Peter J. Janneta
Pawel J. Jastreboff
Peter Jebsen
Herman A. Jenkins
Niels F. Jensen
James Jerger
Anto M. Jetton
Alan Johnson
Jonas T. Johnson
Steven K. Juhn
Timothy T. K. Jung
Charles Jungreis
Gerry Kahn
Peter Kahridas
Larry R. Kaiser
Donald B. Kamerer
Fuminori Kanaya
Michael P. Karnell
Haskins Kashima
Jan Kasperbauer
Peter Kaufman
Kevin Kavanaugh
Robert Keith
Marly Kenna
David W. Kennedy
Eugene Kern
Paul R. Kileny
W. J. Kimberline
Robert Kimura
Sam E. Kinney
John A. Kirchner
Karen Kirk
Jerome O. Klein
Sjaak Klis
John F. Knutson
Robert Kohut
Franklin P. Koontz
James F. Koufman
Timothy F. Kresowik
Arvind Kumar
Ollivier Laccourreye
Peter R. Laibson
Anil K. Lalwani
Susan E. Langmore
Charles R. Larson
J. P. Laurent
Merle Lawrence
Stanley G. Lesinski
Kevin O. Leslie
Sam Levey
Howard Levine
Jean Lewis
James Lighthill
David J. Lim
Andrew N. Lin
Frederick H. Linthicum
Brenda L. Lonsbury-Martin
Anders Lovqvist
Frank E. Lucente
Christy L. Ludlow
Charles M. Luetje
Valerie J. Lund
Lars Lundblad
Erich S. Luschei
Rodney P. Lusk
Caroline Lynas
Richard Lynch
Dennis R. Maceri
Bruce Maddern
Bengt Madison
Roger D. Madison
Anthony Magit
Eric A. Mair
Leslie Malmgren
Anthony Mancuso
Anthony J. Maniglia
Scott Manning
Nicholas Maragos
R. J. Marchbanks
Robert H. Margolis
Bernard Marsh
Sudu Masaharu
Robert H. Mathog
Douglas Mattox
Richard Maw
E. James Maxey
Mark May
Nina A. Mayr
Thomas McCaffrey
Fred M. S. McConnel
Timothy M. McCulloch
Thomas J. McDonald
William F. McGuirt
Pedro Melina-Negro
Arnold H. Menezes
Ulf Mercke
William L. Meyerhoff
Marian Michaels
Olaf Michel
Samuel Mickelson
John C. Middlebrooks
Josef M. Miller
Richard T. Miyamoto
Goro Mogi
Aage R. Moller
William W. Montgomery
Robert Morecraft
William H. Moretz
Nozomu Mori
Hughlett L. Morris
Andrew W. Morrison
Richard A. Moscicki
J. B. Mulliken
Harlan R. Muntz
Jeffrey C. Murray
Joseph A. Murray
Frank Muziek
Eugene N. Myers
Robert Naclerio
Joseph B. Nadol, Jr
Lewis M. Nashner
Julian M. Nedzelski
Gail Neely
R. Netsell
Richard D. Nichols
John Niparko
Yasuya Nomura
Karin Nylander
Paul O'Flynn
Pearay L. Ogra
Hirofumi Ohashi
Dennis P. O'Leary
Kerry Olsen
Nels R. Olson
Dov Ophir
Robert H. Ossoff
Catherine Palmer
William R. Panje
Michael M. Paparella
Dennis G. Pappas
Simon C. Parisier
Lorne S. Parnes
Steven M. Parnes
Desidero Passali
Bruce Pearson
Myles Pensak
Bice Perussia
Phillip K. Peterson
Jay Piccirillo
Thomas Platts-Mills
Charles E. Platz
Christopher Post
Seth Pransky
Jiri Prazma
John P. Preece
D. J. Premachandra
S. S. Prine
Leonard Proctor
Ilmari Pyykko
Yehoash Raphael
Jacqueline Raymond
Miriam I. Redleaf
Herbert Reichelmann
James Reilly
Kent Remily
Tianying Ren
Dale H. Rice
Hal B. Richerson
William J. Richtsmeier
Frank Rimell
Frank N. Ritter
K. Thomas Robbins
Robert A. Robinson
Robert L. Rodnitzky
Clark Rosen
Richard Rosenquist
Allen D. Roses
James A. Royall
Robert J. Ruben
Jay T. Rubenstein
Laurence A. Rubin
Michael J. Ruckenstein
Allen F. Ryan
Jai Ryu
Diane Sabo
Jacob Sade
Tetsushi Sakashita
Tuulo Salo
Isamu Sando
Clarence T. Sasaki
Robert T. Sataloff
Yutaka Sato
William H. Saunders
Franklin Scamman
Steven D. Schaefer
Barry Schaitkin
Stimson P. Schantz
Volker Schilling
Stephanie Schmitz
Victor Schramm, Jr
David E. Schuller
Konrad S. Schulze
Donald J. Schum
Allan Seid
Roy B. Sessions
Andrew Shapiro
Stanley Shapshay
Gail Sheehy
Neil T. Shepard
Karl H. Siedentop
Herbert Silverstein
F. Blair Simmons
Richard J. Sinard
Mark I. Singer
J. H. Sisson
Valdemar Skoog
R. W. T. Slack
Elaine M. Smith
Richard J. H. Smith
Shelley D. Smith
W. D. A. Smith
Carl Snyderman
Nancy Pearl Solomon
Peter Som
Gershon J. Spector
David R. Springall
Heinz Stammberger
James Stankiewicz

Robert Stanley
Lewis D. Stegink
Robert E. Stone
Sylvan E. Stool
Brad J. Story
Robert Strickland
Junichi Suzuki
K. Svartengren
Douglas Swarts
Haruo Takahashi
Yoav P. Talmi
Jun Tamaoki
M. Eugene Tardy
Stanley Thawley
J. Regan Thomas
Donna K. Thompson
Lester Thompson
Aaron Thornton
Ingo R. Titze
Orjan Tjernstrom
Dean M. Toriumi
Mirko Tos
Michael Trudeau
Harvey M. Tucker
Richard S. Tyler
E. Krishnan Unni
Mark L. Urken
Alain Uziel
Galdino E. Valvassori
John C. VanGuilder
Jan E. Veldman
Katherine Verdolini
Jack A. Vernon
Eugenia M. Vining
R. VonBaumgarten
Hans von Leden
Richard L. Voorhees
Donald Vrabec
Phillip A. Wackym
Michael Wall
Thomas Walschmidt
Adam Wanner
Lou Weiland
Jane L. Weisman
Robert Weisman
D. Bradley Welling
Ursula Wells
Louis W. Welsh
Bruce M. Wenig
Jay Werkhaven
Max Wertz
Stephen J. Wetmore
Ernest A. Weymuller, Jr
Richard J. Wiet
Frederic L. Wightman
G. H. Williams
Mary Wilson
Howard Winfield
John R. Wingard
Gerald Wolf
L. B. Wong
Gayle Woodson
Kohichi Yamamoto
N. Yanagihara
Eiji Yanagisawa
Robert Yellon
T. J. Yoo
Devin Yu
William T. C. Yuh
George Zalzal
H. B. Zampe
Steven Zeitels
Deborah Zeitler
Ken Zhen
Richard Zimmerman

SUPPLEMENT 177 — APRIL 1999
Volume 108, Number 4, Part 2

CLINICAL RESULTS WITH THE CLARION® MULTI-STRATEGY™ COCHLEAR IMPLANT

Editors

MARY JOE OSBERGER, PHD
DAWN BURTON KOCH, PHD

ANNALS
OF OTOLOGY,
RHINOLOGY &
LARYNGOLOGY

PREFACE

Over the last 25 years, it has been established clearly that adults and children with severe-to-profound hearing impairments experience substantial benefits from cochlear implants. Those benefits have improved significantly as new technologies developed. For example, the benefits associated with the first commercially available single-channel implants were limited to detecting sound and assistance with lipreading. After the first multichannel devices were introduced, patients began to experience excellent lipreading enhancement, identification of vowels, consonants, and words in a closed set, and some open-set sentence recognition. Today's technology has resulted in levels of performance that were unimaginable 2 decades ago. Most current adult implant users can converse on the telephone and listen to music. Prelingually deafened children demonstrate high levels of auditory-only speech recognition, along with improved speech production and language abilities. The expansion of the population that may benefit from cochlear implantation is predicated on the high degree of success experienced by users of today's implant technology.

This supplement presents clinical results obtained with the CLARION® Multi-Strategy™ Cochlear Implant. The Clarion device is the result of the collaborative effort of researchers at the University of California, San Francisco, Research Triangle Institute, and Advanced Bionics Corporation, a company with extensive experience in the development of implantable medical devices. The company's experience in implantable prostheses and miniaturization has steered the direction and development of innovative cochlear implant technology since the Clarion device was introduced in 1991. Subsequent commercial distribution approval was granted by the US Food and Drug Administration in 1996 for adults and in 1997 for children. To date, the Clarion is the only cochlear implant system with multiple independent output circuits, continuous bidirectional telemetry, and the capability of producing both simultaneous and nonsimultaneous stimulation with either analog or pulsatile stimulation.

The articles in this supplement describe the Clarion system and report results and benefits experienced by adults and children. Contributions have been made by surgeons and audiologists at leading research institutions, as well as by the scientific staff of Advanced Bionics Corporation. The articles address a wide range of important clinical issues, including the use of objective measures for device programming; longitudinal speech perception, production, and language results in children; a comparison of children's performance with implants, hearing aids, and different implants; benefits derived by special populations; predictors of postimplant performance; and the results of recently introduced advances in speech processing.

The contributions of the authors and of Dawn Burton Koch, PhD, who served as guest co-editor, are gratefully acknowledged. In addition, we are deeply indebted to the Clarion users and to their families for their willingness to participate in the clinical studies presented in this publication.

Mary Joe Osberger, PhD
Director, Clinical Research
Advanced Bionics Corporation
12740 San Fernando Road
Sylmar, CA 91342

UNIVERSITY
LIBRARY

COPYRIGHT© 1999, ANNALS PUBLISHING COMPANY, 4507 LACLEDE AVENUE, ST LOUIS, MO 63108

CONTENTS

Preface
Mary Joe Osberger, PhD 1

Introduction. Personal Reflections on Cochlear Implants
Robert A. Schindler, MD 4

Description of the CLARION® Multi-Strategy™ Cochlear Implant

The CLARION® Multi-Strategy™ Cochlear Implant
Dorcas K. Kessler, MA 8

Programming Features of the CLARION® Multi-Strategy™ Cochlear Implant
Susan Zimmerman-Phillips, MS; Carol Murad, MSc 17

Clinical Results of the CLARION® Magnetless Cochlear Implant
Benno P. Weber, MD, PhD; Jürgen Neuburger, MD; Jenny E. Goldring, MSc; Thomas Santogrossi, BEng; Herbert Koestler, PhD; Rolf D. Battmer, PhD; Thomas Lenarz, MD, PhD 22

Surgical Procedures With the CLARION® Multi-Strategy™ Cochlear Implant

Surgical Technique for the CLARION® Cochlear Implant
Thomas J. Balkany, MD; Noel L. Cohen, MD; Bruce J. Gantz, MD 27

Using the CLARION® Cochlear Implant in Cochlear Ossification
Philip A. Bird, MD; Thomas J. Balkany, MD; Annelle V. Hodges, PhD; Stacy Butts, MA; Orlando Gomez, PhD; David Lee, PhD 31

Implantation of the CLARION® Cochlear Implant in an Ossified Cochlea
Lee A. Harker, MD; Deborah Veazey, MS; Natalie Gentile, MA; Elizabeth McCleary, MA 35

Multichannel Cochlear Implantation in Children With Large Vestibular Aqueduct Syndrome
Lee A. Harker, MD; Scott Vanderheiden, MD; Deborah Veazey, MS; Natalie Gentile, MA; Elizabeth McCleary, MA 39

Cochlear Implantation in Children Under the Age of Two: The MHH Experience With the CLARION® Cochlear Implant
Thomas Lenarz, MD, PhD; Anka Lesinski-Schiedat, MD; Sabine von der Haar-Heise; Angelika Illg; Bodo Bertram; Rolf D. Battmer, PhD 44

Objective Testing With the CLARION® Multi-Strategy™ Cochlear Implant

Relationship Between EABR Thresholds and Levels Used to Program the CLARION® Speech Processor
Carolyn J. Brown, PhD; Michelle L. Hughes, MA; Susan M. Lopez, MA; Paul J. Abbas, PhD 50

Electrically Evoked Potentials Recorded in Adult and Pediatric CLARION® Implant Users
Jill B. Firszt, PhD; Lee Ann Rotz, MA; Ron D. Chambers, PhD; Michael A. Novak, MD 58

Using Electrically Evoked Auditory Reflex Thresholds to Fit the CLARION® Cochlear Implant
Annelle V. Hodges, PhD; Stacy Butts, MA; Shelly Dolan-Ash, MS; Thomas J. Balkany, MD 64

Clinical Results With the CLARION® Multi-Strategy™ Cochlear Implant in Adults

Simultaneous Analog Stimulation (SAS)–Continuous Interleaved Sampler (CIS) Pilot Comparison Study in Europe
Rolf D. Battmer, PhD; Yitzak Zilberman; Philip Haake, MD; Thomas Lenarz, MD, PhD 69

SAS-CIS Preference Study in Postlingually Deafened Adults Implanted With the CLARION® Cochlear Implant
Mary Joe Osberger, PhD; Laurel Fisher, PhD 74

The Effect of Long-term Deafness on Speech Recognition in Postlingually Deafened Adult CLARION® Cochlear Implant Users
Lisa Geier, MA; Mary Barker, MS; Laurel Fisher, PhD; Jane Opie, PhD 80

Implantation of Patients With Prelingual Long-term Deafness
Susan B. Waltzman, PhD; Noel L. Cohen, MD 84

Clinical Results With the CLARION® Multi-Strategy™ Cochlear Implant in Children

Clinical Trial of the CLARION® Cochlear Implant in Children
Mary Joe Osberger, PhD; Susan Zimmerman-Phillips, MS; Mary Barker, MS; Lisa Geier, MA 88

Speech Perception Results for Children Implanted With the CLARION® Cochlear Implant at the Medical University of Hannover
Angelika Illg; Sabine von der Haar-Heise; Jenny E. Goldring, MSc; Anka Lesinski-Schiedat, MD; Rolf D. Battmer, PhD; Thomas Lenarz, MD, PhD 93

Speech Perception of Young Children Using Nucleus 22-Channel or CLARION® Cochlear Implants
Nancy M. Young, MD; Kristine M. Grohne, MA; Vincent N. Carrasco, MD; Carolyn Brown, MS 99

Comparison of Speech Perception in Pediatric CLARION® Cochlear Implant and Hearing Aid Users
Mario A. Svirsky, PhD; Ted A. Meyer, MD, PhD 104

Speech Production Results in Children Implanted With the CLARION® Implant
Carolyn Brown, MS; Deborah W. McDowall, MA 110

Language Development in Children Implanted With the CLARION® Cochlear Implant
Amy McConkey Robbins, MS; Priscilla M. Bollard, EdD; Janet Green, MS 113

Specific Language Growth in Young Children Using the CLARION® Cochlear Implant
Priscilla M. Bollard, EdD; Patricia M. Chute, EdD; Amy Popp, MS; Simon C. Parisier, MD 119

Meta-Analysis of Pediatric Cochlear Implant Literature
André K. Cheng, MD; Ginger D. Grant, MS; John K. Niparko, MD 124

INTRODUCTION
PERSONAL REFLECTIONS ON COCHLEAR IMPLANTS

ROBERT A. SCHINDLER, MD
SAN FRANCISCO, CALIFORNIA

Cochlear implants represent a classic example of a "scientific revolution." According to Kuhn,[1] scientific disciplines undergo periods of "normal science" in which they obtain a high degree of precision and progress rapidly. Normal science is dependent on the adoption of a universally accepted paradigm that defines research problems for the scientist and provides the methods that should be applied to solve them. However, in the course of research, scientists inevitably stumble upon anomalies in the existing paradigm. Eventually, a competing theory proves relatively successful in explaining the anomaly, and the old paradigm is modified and replaced with a new paradigm. It is this process that defines a "scientific revolution." Initially, the scientific community resists the replacement, but with time and successful application, the new paradigms gain enough support to win acceptance. In turn, the new paradigm creates new research questions, new methodologies, and new results.

To understand the nature of the scientific revolution that cochlear implants exemplify, we need to return to the early 1970s. In June 1973, a meeting was held at the University of California–San Francisco (UCSF) entitled "First International Conference on Electrical Stimulation of the Acoustic Nerve as a Treatment for Profound Sensorineural Deafness in Man." It was the first scientific gathering ever held to discuss cochlear implants. Prior to this conference, the public, the deaf community, and most physicians were largely unaware of these devices. Auditory physiologists and histopathologists dismissed them as misguided attempts by surgeons — who knew little or nothing about auditory neuroscience — to stimulate nerves that were already dead. Further, if they were not dead prior to inserting electrodes into the cochlea, they were certain to be dead after implantation. Ingrained in the scientific orthodoxy of the time was the belief that if cochlear hair cells died, then neurons also would necessarily degenerate.

Before the 1973 meeting, only 1 publication suggested that cochlear implant systems could be built reliably for humans and provide useful sound sensations to deaf patients. By the time of the conference, House and Urban[2] reported that their single-channel implant system was providing useful hearing to profoundly deaf subjects. Despite those reports, Merle Lawrence, PhD, then head of the Kresge Hearing Research Institute at the University of Michigan, summarized the prevailing attitudes of the scientific community when he stated that it would be impossible for a cochlear implant to replicate the complexities of the organ of Corti in order to produce speech understanding. "Regardless of the number of channels or electrode points, normal frequency specificity cannot be achieved."[3(p28)] In other words, frequency-specific stimulation, regardless of the number of electrodes or their location within the cochlea, could never be accomplished. All that would be produced, he reasoned, would be noise, and even then, the dynamic range was liable to be extremely limited.[3] Harold Schuknecht, MD, Professor and Chairman of the Department of Otolaryngology at Harvard and a noted cochlear histopathologist, was more direct when he stated, "I will admit that we need a new operation in otology, but I am afraid this is not it."[3(p209)]

In spite of this prevailing attitude, cochlear implant research and development continued among small groups of investigators that were active at the time of the 1973 conference. They included Robin Michelson, Michael Merzenich, myself, and our associates at UCSF; William House and Jack Urban at the House Ear Institute in Los Angeles; F. Blair Simmons and Robert White at Stanford University; Donald Eddington at the University of Utah; Henri Chouard in France; and Graeme Clark in Australia. Other than these few physicians and scientists, the emerging cochlear implant technology was either ignored or dismissed as unlikely to produce a useful hearing device.

The dismissal of cochlear implants had its basis in historical events. Ever since 1800, when Volta[4] reported that passing an electrical current through the ears caused an audible sound, scientists had hoped to use electricity to restore hearing. Little happened until 2 classic experiments were reported in the early part of this century. In 1925, radio engineers discovered the "electrophonic hearing" effect, noting that sound could be produced by electrically stimulating electrodes in the near vicinity of the ear.[5] This report was followed in 1930 by one of the most exciting experiments in the history of auditory neuroscience. Wever and Bray[6] accidently discovered that

---

CORRESPONDENCE — Robert A. Schindler, MD, Department of Otolaryngology, University of California–San Francisco, 400 Parnassus Ave, Rm A-730, San Francisco, CA 94143.

researchers speaking near an anesthetized cat's ear could be distinctly heard on a loudspeaker in an adjoining room via an electrode surgically placed on the auditory nerve. They had discovered a phenomenon known as the "cochlear microphonic," an electrical potential arising from the cochlea as a result of acoustic stimulation. Their discovery gave rise to the hypothesis that the transmission of sound from the cochlea to the brain was analogous to a telephone, with the cochlear hair cells responsible for converting sound into an electrical analog that traveled along the auditory nerve to the brain.

Even though the hypothesis was eventually proven incorrect, Wever and Bray's[6] findings suggested to some scientists that there was a possibility that hearing could be restored by stimulating the eighth nerve with an electrical analog of sound. Djourno and Eyries[7] published the first data on direct stimulation of the auditory nerve in a totally deaf person in the mid-1950s. During a reoperation for facial paralysis in a 50-year-old man who had undergone a radical mastoidectomy for cholesteatoma that had destroyed the cochlea, an inductively coupled electrode was placed into the stump of the remaining nerve and a current was delivered via a primitive speech processor. The patient heard sounds like "crickets" or a "roulette wheel." This research report attracted the attention of several surgeons in the United States and prompted them to investigate the feasibility of producing a device that would allow the profoundly deaf to hear. These surgeons included Drs James Doyle, William House, F. Blair Simmons, and Robin P. Michelson, each working in California at 3 independent facilities.

In 1961, William House and James Doyle designed a few implantable cochlear stimulating devices based on the work of the scientists at Massachusetts Institute of Technology and in the Soviet Union, and tested them in human patients. Due to limited understanding regarding the construction of an electronic implant, leakage, and the toxic nature of some of the implant materials, they were forced to remove the devices after several weeks when the implant sites became inflamed. Nevertheless, House and Doyle's initial results indicated that patients could perceive the rhythm of speech and music and were aware of a variety of environmental sounds.[8] Unfortunately, the technical difficulties they encountered reinforced the scientific belief that attempts to build a useful cochlear implant were doomed to fail.

The failure of the Doyle device was followed by an extensive assessment of the feasibility of cochlear implantation. At Stanford University, F. Blair Simmons placed an electrode into the modiolus of the cochlea of a terminally ill, congenitally deaf patient and demonstrated that the patient could perceive some sound when stimulated. Disappointed that the patient could not understand speech, Simmons stated that the chances were small that electrical stimulation of the auditory nerve could ever provide a useful means of communication.[9] Negative opinions of cochlear implants were once again reinforced.

When Robin Michelson[10] presented and published data on the first successful series of patients implanted with a single-channel cochlear implant, the prevailing negative views were dispelled and the scientific revolution truly was launched. Michelson obtained independent grant funding from the Department of Defense and brought his cochlear implant program to UCSF. He believed that a transcutaneous implanted receiver, with bipolar electrodes placed in the scala tympani close to the modiolus, would provide the best chance of delivering electrical signals to the auditory neurons. He tested preliminary devices in animals and became convinced that there was a real possibility of restoring hearing if the cochlear microphonic could be simulated. By the late 1960s, with the assistance of Arnold Beckman and Mel Bartz, he had constructed a device with biocompatible materials that could be implanted in human patients. Michelson's cochlear implant system consisted of a single-channel processor that converted speech into an electrical analog that was inductively coupled to an implanted passive receiver and bipolar scala tympani stimulating electrodes. The electrodes were covered in silicone and molded to fit into the basal scala tympani via a cochleostomy anterior to the round window. This system was implanted in 4 patients, and his report of their hearing results represents a watershed for clinically applicable cochlear implants.

The cochlear implant scientific revolution was launched with Robin Michelson's presentation entitled "The Results of Electrical Stimulation of the Cochlea in Human Sensory Deafness" to the American Otological Society, Inc, in May 1971. The discussion of this paper by distinguished members of the scientific establishment details their shock and complete disbelief in Michelson's results. His data were in direct conflict with existing concepts in auditory neuroscience and engendered extreme skepticism. Nonetheless, cochlear implant research and development expanded at UCSF. In 1971, Michael Merzenich and I joined Michelson in his work. Our objective was to understand what, why, and how patients heard with the Michelson implant and then to develop a strategy for building a multichannel system. The ultimate goal was the development of a device that could provide speech understanding to totally deaf patients.[11] A series of animal studies and subsequent human investigations resulted in progressive improvements of a multichannel cochlear implant.

By June 1973, at the time of the First International Conference on Cochlear Implants in San Francisco, House had implanted 12 patients, Michelson and his colleagues had implanted 7 patients (1 still has a functioning unit as of this writing), and Simmons had implanted 2 patients. In spite of the modest initial success reported by each of these 3 groups, as well as by Chouard in France, the application of cochlear implants in deaf patients continued to meet with strong resistance in the scientific community. Scientists had 2 major ethical concerns about human implantation. First, they believed that safety and efficacy data could be obtained from animal experimentation. Second, they believed that the device itself could never work because of extensive and irreversible neural damage present in deaf individuals. In addition to these concerns, extravagant anecdotal claims began surfacing in public, including subjective patient testimonials about hearing birds again and enjoying music. This publicity further alienated the scientific community. Cochlear implant researchers were regarded as the pariahs of the academic community.[3]

Undaunted by criticism, William House introduced the first widely applied clinical cochlear implant in 1973. This implant was a single-channel system that was later commercialized and manufactured by 3M and became known as the 3M/House implant. The device was implanted by many surgeons in hundreds of deaf adults and children throughout the world before 3M stopped production. Little progress in implantation would have been made without those pioneering efforts.

Much of the early cochlear implant work was supported by the National Institutes of Health (NIH), whose grants and contract programs facilitated implant development. This funding was encouraged especially by Terry Hambrecht of the then National Institute of Neurological and Communicative Disorders and Stroke, whose vision and belief propelled cochlear implant technology forward to the point at which implant recipients now hear and understand speech. In October 1974, the NIH sponsored a Cochlear Implant Workshop at UCSF to review the status of cochlear implants and to define the requirements for a multichannel device. The NIH not only sponsored basic research, but also was instrumental in developing clinical research programs. Notably, the NIH supported the first independent, multicenter study of cochlear implant devices. Led by R. C. Bilger at the University of Pittsburgh, the study concluded that these devices were a definite aid in communication, particularly when combined with lipreading, and were also useful in voice modulation and recognition of environmental sounds.[12] More important, the 1977 study provided substantial scientific evidence for the benefits of cochlear implantation and gave credibility to the emerging technology.

In 1981, 2 groups — Michelson and Schindler[13] at UCSF and Clark et al[14] at the University of Melbourne — reported the first useful speech discrimination in cochlear implant patients. It is of note that each group used a different implant device to achieve their results.

In 1983, 10 years after the first conference on cochlear implants, a Tenth Anniversary Conference on Electrical Stimulation of the Ear was held at UCSF. Instead of the skepticism and controversy that permeated the first conference, optimism prevailed. Fourteen active research centers were represented, and over 1,000 devices had been implanted worldwide.

Research and development of cochlear implants has continued. To date, 3 devices have been released by the US Food and Drug Administration for commercial marketing in this country. The first was the 3M/House single-channel cochlear implant (initially approved in 1984). The second was the Nucleus 22-channel cochlear implant, approved in 1985 for adults and in 1990 for children. The third was the CLARION® Multi-Strategy™ Cochlear Implant, which was approved for adults in 1995 and for children in 1997. In addition, a fourth cochlear implant system, the Med-El Combi 40+, is undergoing clinical trials. These implant systems are far more sophisticated than those of a decade ago. They accommodate a variety of speech processing strategies and stimulation modes to address the individual needs of hearing-impaired patients.

For physicians interested in the benefits of implantation, the advent of competition in the industry is the most encouraging aspect in the history of cochlear implant development since its initial acceptance as a viable rehabilitative tool. As a co-developer of one of the first successful multichannel devices, I found that the inherent limitations of a university research facility in fabricating a sophisticated cochlear implant device became apparent. Although a university is ideal for testing ideas and developing prototypes, we must turn to industry for the manufacture of safe and reliable human implants. To further advance the field, these companies must have strong engineering expertise and a commitment to research and development. Given these requirements, it is no surprise that the 2 most successful cochlear implant manufacturers evolved from the cardiac pacemaker industry.

The university-based research team often finds it difficult to know when the time has come to give up control of their project, to talk to their office of technology transfer or patent office, and to request assistance in transferring core technology to an outside company. At UCSF in the mid-1980s, we had the assistance of the Storz Instrument Company in building the UCSF/Storz cochlear implant. That cooperative effort provided the opportunity to study multichannel stimulation in 16 patients implanted with that device between 1985 and early 1986. Speech recognition in these patients was very good, but design flaws related to the disconnect system led to direct current leakage in several patients, necessitating discontinuation of the device.[15-17] It became apparent to both Storz and UCSF that significantly more engineering and financial resources than had been anticipated would be required to commercialize the multichannel system we envisioned.

In October 1985, at the NIH Neural Prosthesis Program meeting held annually in Bethesda, Maryland, UCSF presented data on the Storz patients. There we met Joseph Schulman of the Alfred E. Mann Foundation and explained our acute need for assistance to make the quantum leap from the Storz device to a small, hermetically sealed 8-channel system that could handle both analog and pulsatile stimulation in either bipolar or monopolar modes. Schulman suggested that we present our research to the leadership of a new research and development company, Minimed Technologies, that was headed by Alfred E. Mann, founder of Pacesetter Systems, the second largest cardiac pacemaker manufacturer in the world. Encouraged by this interest, I met with Al Mann and his team in spring 1986 in Sylmar, California, and presented the results achieved with the Storz device. When I showed a videotape of how well 3 of the patients heard with the device, and how they described their experiences, Al was moved to tears. He congratulated us on our work and inquired how much money would be needed to build and launch a new 8-channel system. I responded, "About $10 million." Al said, "Maybe, but I'll bet more." And then he said, "If you can get the university to take a reasonable royalty, I'll fund the project myself — my own money. That way I know it will get done." As I sat on the plane on my return to San Francisco, looking down at the rapidly shrinking San Fernando Valley, I felt my own tears. Finally — after all the struggles, all the failures, all the false starts — there was someone who could make it happen. The papers that follow are a direct result of Al Mann's commitment to his word, to the deaf, and to the dreams of all the early cochlear implant pioneers.

ACKNOWLEDGMENTS — So many people have contributed to the development and success of cochlear implants, it is impossible to mention them all. You know who you are, and the world owes you thanks. But it is Robin Michelson and his great contributions that I wish to acknowledge especially. He was my mentor, colleague, and dear friend for more than 27 years, and he deserves credit for giving birth to the cochlear implant revolution that began in May 1971.

REFERENCES

1. Kuhn TS. The structure of scientific revolutions. Chicago, Ill: University of Chicago Press, 1962.
2. House WF, Urban J. Long term results of electrode implantation and electronic stimulation of the cochlea in man. Ann Otol Rhinol Laryngol 1973;82:504-17.
3. Merzenich MM, Schindler RA, Sooy FA, eds. Proceedings of the First International Conference on Electrical Stimulation of the Acoustic Nerve as a Treatment for Profound Sensorineural Deafness in Man. San Francisco, Calif: University of California, 1974.
4. Volta A. On the electricity excited by the mere contact of conducting substances of different kinds. Trans R Soc Phil 1800;90:403-31.
5. Steven SS, Jones RC. The mechanism of hearing by electrical stimulation. J Acoust Soc Am 1939;10:261-9.
6. Wever EG, Bray CW. The nature of the acoustic response: the relation between sound frequency and frequency of impulses in the auditory nerve. J Exp Psychol 1930;13:373-87.
7. Djourno A, Eyries C. Prothese auditive par excitation electrique a distance du nerf sensoriel a l'aide d'un bobinage inclus a demeure. Presse Med 1957;35:14-7.
8. Doyle JH, Doyle JB, Turnbull FM Jr. Electrical stimulation of the eighth cranial nerve. Arch Otolaryngol 1964;80:388-91.
9. Simmons FB. Electrical stimulation of the auditory nerve in man. Arch Otolaryngol 1966;84:2-54.
10. Michelson RP. The results of electrical stimulation of the cochlea in human sensory deafness. Ann Otol Rhinol Laryngol 1971;80:914-9.
11. Michelson RP, Merzenich MM, Schindler RA, Schindler DN. Present status and future development of the cochlear prosthesis. Ann Otol Rhinol Laryngol 1975;84:494-8.
12. Bilger RC, Black FO. Auditory prostheses in perspective. Ann Otol Rhinol Laryngol [Suppl] 1977;86(suppl 38):3-10.
13. Michelson RP, Schindler RA. Multichannel cochlear implant: preliminary results in man. Laryngoscope 1981;91:38-42.
14. Clark GM, Tong YC, Martin LF. A multiple channel cochlear implant: an evaluation using open-set CID sentences. Laryngoscope 1981;91:628-34.
15. Schindler RA, Kessler DK, Rebscher SJ, Jackler RK, Merzenich MM. Surgical considerations and hearing results with the UCSF/Storz cochlear implant. Laryngoscope 1987;97:51-6.
16. Schindler RA, Kessler DK. The UCSF/Storz cochlear implant: patient performance. Am J Otol 1987;8:247-55.
17. Schindler RA, Kessler DK. State of the art of cochlear implant: the UCSF experience. Am J Otol 1989;10:79-83.

Ann Otol Rhinol Laryngol 108:1999

THE CLARION® MULTI-STRATEGY™ COCHLEAR IMPLANT

DORCAS K. KESSLER, MA
SYLMAR, CALIFORNIA

The Clarion cochlear implant is the result of many years of research and development, first at the University of California, San Francisco and the Research Triangle Institute of North Carolina, and then at Advanced Bionics Corporation in Sylmar, California. Approved by the US Food and Drug Administration after carefully monitored investigational clinical trials in both the adult and pediatric populations, it has now been implanted in approximately 3,000 patients worldwide. A fully flexible, programmable system, the Clarion offers multiple strategies and options in speech processing. The coupling mode, the stimulating waveform, and the temporal pattern of stimulation can be selected to allow each patient an opportunity to be fitted with the strategy that offers the highest level of performance. This paper describes the current status of the Clarion system. However, Clarion development has been a dynamic process, and from its initial introduction in 1991, the system has been modified and continually improved. The process of improvement and advancement is ongoing. New speech processing strategies and hardware developments are briefly summarized at the conclusion of this paper.

KEY WORDS — cochlear implant.

INTRODUCTION AND HISTORICAL BACKGROUND

The first clinical application of the CLARION® Multi-Strategy™ Cochlear Implant occurred in March 1991. The Clarion was approved for commercial distribution in adults in March 1996, and in June 1997, it was approved for use in the pediatric population. At the time of this writing, approximately 3,000 patients worldwide, including both children and adults, have been implanted with the Clarion. Since its initial introduction in 1991, the device has undergone both internal and external modifications, each change improving its functionality and resulting in increased patient benefit. With each device modification, the design objectives and principles that informed the development of the original Clarion have been consistently implemented. These design goals include the production of a safe and reliable device and the application of innovative, advanced technology. In addition to these objectives that are shared by all manufacturers of cochlear implants and other implantable medical devices, the Clarion was designed with the understanding that each patient is unique and that the same speech processing scheme cannot yield the same performance for all subjects. The Clarion's architecture is engineered so that each patient can be fitted with a processing strategy that offers the individual the greatest opportunity for speech recognition.

Development of the Clarion began in 1987 with the cooperative efforts of 3 organizations: the Department of Otolaryngology of the University of California, San Francisco (UCSF), the Center for Auditory Prosthesis Research of the Research Triangle Institute, North Carolina (RTI), and Advanced Bionics Corporation (then MiniMed Technologies, Inc). Supported by various US National Institutes of Health grants and contracts, UCSF and RTI had worked collaboratively since 1983, with RTI contributing expertise in speech processing strategies and UCSF providing expertise in the design and construction of intracochlear electrodes, biocompatibility, and safety. To this blend, Advanced Bionics added engineering expertise and experience in the manufacture of cardiac pacemakers and implantable neurostimulators. The Clarion thus benefited from a combination of diverse skills and talents.

As work proceeded, Advanced Bionics also had the advantage of historical hindsight. Almost 2 decades of cochlear implant application were available for review at the time Clarion development began. A survey of implant technology at that time revealed that to some extent, every form of processing was viable and resulted in some degree of patient benefit. The only exception to this finding concerned single-channel devices, for which various studies had demonstrated the superiority of multichannel stimulation.[1,2] Therefore, a single-channel system was never regarded as a viable option. Because there are no definitive preoperative measures, either electrophysiological or radiographic,[3,4] that can predict treatment outcome or guide processor selection, a key design objective emerged: the development of a multichannel device whose engineering would support speech processing options.[5,6] Rather than discard a potentially useful tool, it was deemed critical to pro-

---

From Advanced Bionics Corporation, Sylmar, California.

CORRESPONDENCE — Dorcas K. Kessler, MA, Advanced Bionics Corporation, 12740 San Fernando Rd, Sylmar, CA 91342.

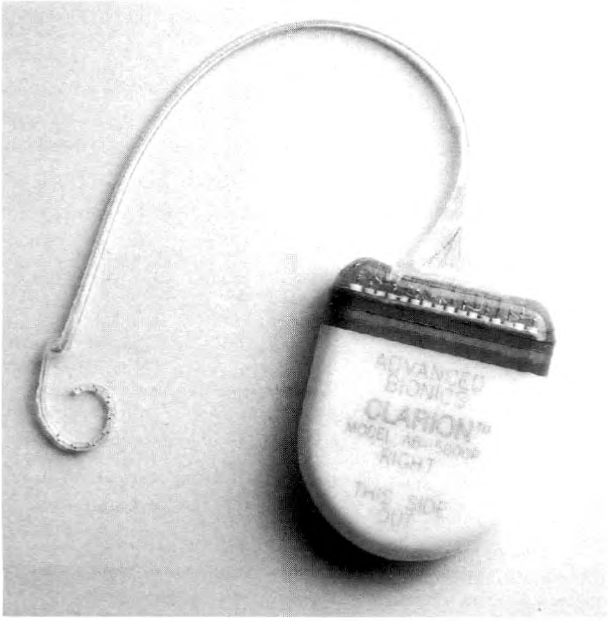


Fig 1. Internal components of Clarion, or Implantable Cochlear Stimulator, consisting of hermetically sealed receiver case, which houses electronic circuitry, antenna, and magnet, and attached intracochlear electrode array.

vide a device that could offer alternatives in stimulation mode (monopolar and bipolar), the stimulating waveform (analog or pulsatile), and the temporal distribution of the signal (simultaneous and nonsimultaneous).

INTERNAL COMPONENTS

The internal portion of the Clarion system is referred to as the Implantable Cochlear Stimulator (ICS). The ICS, shown in Fig 1, consists of 2 parts: the electronic receiver package and the attached intracochlear electrode array.

Intracochlear Electrode Array. The Clarion incorporated the electrode array developed over years of study and research at UCSF.[7,8] This electrode consists of 16 platinum-iridium (90:10) wires that terminate in 16 stimulating contacts held in a molded silicone rubber carrier. The electrode wires are Teflon-coated to insulate them from one another within the carrier, and all the electrode wires are enclosed within a Dacron (polyester) sleeve within the silicone rubber carrier. Each wire is terminated in a 0.3-mm-diameter ball and is positioned in a precise pattern in relation to the overall array in order to achieve optimal excitement of specific regions of the cochlear nerves. The balls, or contacts, are arranged in 8 near-radial bipolar pairs, with a distance of 2 mm between pair centers and a distance of 0.5 mm between the lateral and medial contacts of the bipolar pair. The overall array length is 25 mm, extending from the round window 1 1/2 turns into the cochlea for a maximum insertion depth of 25 mm in a fully patent cochlea. The silicone carrier varies in dimension, conforming to the shape of the scala tympani. The carrier has an elastic memory so that even when inserted, it retains its spiral curve and maintains its position close to the medial (modiolar) wall of the cochlea. The 16 lead wires are stacked in a double-rib configuration that provides maximum flexibility perpendicular to the axis of the cochlea and maximum rigidity parallel to that axis to reduce the potential for insertion trauma and damage to the basilar membrane or bony spiral lamina.

To facilitate placement of the electrode array in the scala tympani, Advanced Bionics developed a unique insertion tool. This tool assists the surgeon by maintaining the electrode array in a straight position during the insertion process. The electrode is inserted into a slender Teflon tube. The tube, with loaded electrode, is mated to the insertion tool, which has a retractable slide. When the slide is advanced, it causes the electrode to move forward, releasing it from the tube and moving it into the scala tympani. As the electrode array is released, it regains its spiral curve. To take advantage of the spiral shape of the array and to ensure that the electrode rounds the first turn, the insertion tool and tube are placed relatively deeply into the basal scala before the electrode is released. The Clarion electrode insertion tool has proven very effective in facilitating electrode insertion, minimizing electrode displacement, and allowing the use of an electrode designed to conform to the modiolar spiral.

Electronic Package. The electronic circuitry, or receiver, is enclosed in a hermetically sealed ceramic case. In the original Clarion, referred to as Version 1.0, the case measured 3.7 × 2.5 × 0.6 cm. In 1995, the device was miniaturized to accommodate placement in young children. This modification, referred to as Version 1.2, significantly reduced the length of the electronic package (to 3.1 cm) by reorganizing the layout of the circuitry and the architecture of the juncture between the receiver and the electrode array. Version 1.2 became available in June 1995 and is the device currently used for both pediatric and adult implantations. The Version 1.2 ICS retains a single ceramic hermetic case, allowing both the electronics and the antenna to be housed together as a single unit, thus eliminating the potential for a disruption between the receiver and the antenna. In both versions, the ICS incorporates a magnet for alignment with the external magnet housed in the headpiece (HP).

Power and data are delivered to the receiver through an inductively coupled link via the external

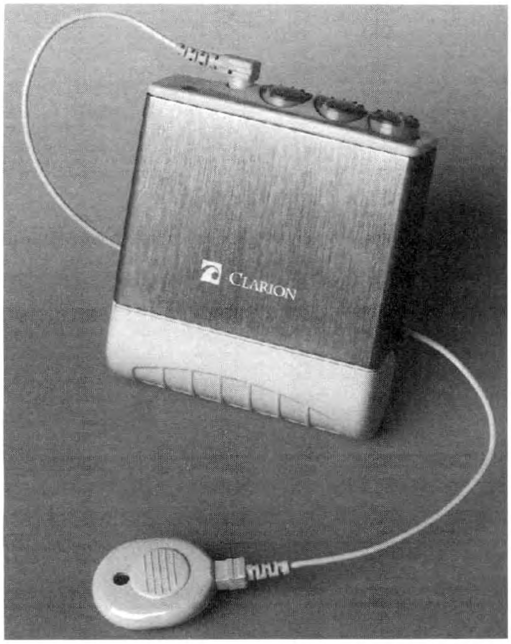


Fig 2. External wearable components of Clarion system, including S-Series speech processor, which houses battery compartment, headpiece, and cable.

antenna. The receiver provides stimulating current to the 16-contact electrode connected to the circuitry through hermetic feed-throughs in the header-case assembly. The delivered energy ranges in output from 1 to 2.5 mA in 255 steps. The output is capacitatively coupled balanced biphasic or monophasic current. The use of capacitors, while taking up valuable space, ensures a relatively safe device that reduces the potential for exposure to direct current. The Clarion's unique flexibility resides in its multiple output circuits. In contrast to other available implant systems that have only a single current source,[9-11] the Clarion has 8 independent circuits. This allows 8 individually powered channels whose stimuli can be programmed independently and configured to drive 16 electrodes plus 1 indifferent electrode in monopolar or bipolar combinations, with analog or pulsatile waveforms, in simultaneous or nonsimultaneous mode. During every frame, each channel can be updated in basal-to-apical, apical-to-basal, or nonsequential order. With all channels operating simultaneously, the overall update rate is 104,000 samples per second, or 13,000 samples per second per channel.

The receiver, or electronic package, sends telemetry information to the external device by means of a 6-bit analog-to-digital converter. Measured parameters include electrode output voltages for electrode impedance measurements and reference voltages to confirm internal device function. Unlike 2-way telemetry systems now available in other implant devices,[10,11] the Clarion enables ongoing monitoring of internal device function because it has 2 independent carrier frequencies: 1 that transmits data to the ICS and 1 that transmits information from the ICS. Data are transmitted to the ICS on an amplitude-modulated (AM) carrier of 49 MHz. Information is received from the ICS (back or reverse telemetry) by means of a frequency-modulated (FM) carrier of 10.7 MHz. Continuous monitoring is a critical safety feature that provides confirmation of device function in very young children who may be unable to report on the status of their cochlear implants.

EXTERNAL COMPONENTS

The external components of the Clarion, shown in Fig 2, include the speech processor (SP), the HP, and the cable. Like the ICS, the SP has evolved over time from the original Version 1.0 processor to the current S-Series processor. Three versions of the SP have been made available: Version 1.0, Version 1.2, and the current S-Series. The size of the SP has been reduced with each new version, and each new SP has resulted in improved patient performance. These improvements are attributed to enhanced engineering and the use of newer components that have allowed a reduction in the signal-to-noise (internal, electronic noise) ratio of the system.

The S-Series processor, released in 1997, is available for children and adults. It has a programmable audio bandwidth ranging from 250 to 6,800 Hz, sends power and data to the passive internal electronics, and is responsible for transmitting speech and environmental sounds to the ICS. It weighs 90 g and is 59 × 69 × 22 mm in size. Sounds are picked up through either a head-level microphone located in the HP or an optional auxiliary lapel-style microphone. The radio frequency–transmitting antenna, housed in the HP, is held in place by a self-locating magnet that couples with the internal magnet in the ICS. Sounds are processed through a bank of bandpass filters into digital information that is transmitted to the ICS for reconstruction and delivery to the patient. Stimulus parameters include either monopolar or bipolar continuous (analog) or discrete (pulsatile) information, or hybrid combinations of these stimulating signals. Individual patient stimulus parameters are retained on an electrical erasable programmable read-only memory chip located in the processor unit. The processor, which houses the battery compartment, is powered by either a rechargeable lithium ion battery pack or 3 standard AA alkaline batteries. It can retain 3 programs concurrently and has 3 user-adjustable controls: a volume control, a sensitivity control, and a program selector switch that also serves as the on-off control. The SP also has an auxiliary input jack for use with the lapel microphone and telephone pickup coil provided

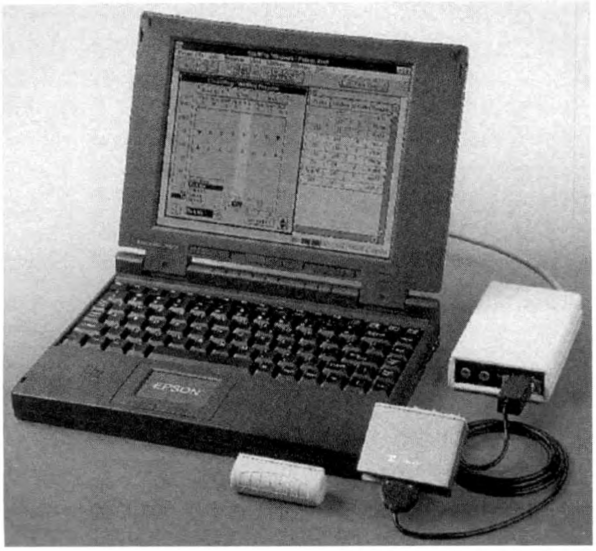


Fig 3. Clarion device-fitting system, including Clinician's Programming Interface, which is attached to serial port of laptop computer and to speech processor via Clinician Programming Interface cable. "Software Clinician" screen (Clarion device-fitting software) is displayed on computer.

with the Clarion system or to connect other external auditory input sources such as battery-powered FM systems, tape recorders, television audio amplifiers, and other assistive listening devices.

Information processed by the SP is transmitted across the HP antenna in a protocol that consists of 9 discrete regions of information per frame interval. The first 8 regions contain amplitude information for control of the 8 output circuits or channels. The ninth region is reserved for command functions. Back telemetry information (ie, data from the ICS transmitted on the FM 10.7-MHz carrier) is formatted in a 1-word-per-frame structure at a rate of 13,000 samples per second. Communication between the ICS and the SP is secured by a "handshake routine" that verifies functionality prior to operating the ICS in the patient application.

The S-Series SP also has several features designed to facilitate its use in the pediatric population. A dual color light-emitting diode (LED) has 3 primary functions: battery charge status, lock status (ie, correct communication between the internal and external components), and microphone system status. Depending on the function, the LED will illuminate with either a red or a green light. When the SP is turned on, the LED light first indicates battery charge status and then lock status. Following completion of this sequence, the microphone system status can be verified. The S-Series also has an optional audible alarm that can be activated at the time of device fitting. This alarm is designed primarily for pediatric users, to alert parents and teachers that the system is not transmitting sound to the implant or that the battery charge is near depletion.

RELATED EQUIPMENT

Several additional pieces of equipment are required to complete the Clarion implant system. A battery charger, an auxiliary microphone, and a telephone adapter are included with each patient set of external equipment. In addition, just as the electrode insertion tool is considered integral for surgical implantation, so, too, the clinician requires a tool that enables verification of device functionality intraoperatively via back-telemetry and tools that are essential for postoperative device programming.

Portable Cochlear Implant Tester. Advanced Bionics has developed a small intraoperative tester, known as the Portable Cochlear Implant Tester (PCIT), which verifies device functionality during the surgical procedure. The PCIT administers a rapid electronic diagnosis of the ICS, providing a simple "link–no link" message. It also allows for the measurement of electrode impedances on each of the 16 electrodes, confirming integrity of the electrode array. In addition, the PCIT has the capability of transmitting a 1,000-Hz sine burst and, in the immediate postoperative period, can serve a third function of determining the patient's responsiveness on each channel. This response–no response behavioral test provides a mechanism for informally evaluating the patient's initial reaction to electrical stimulation and serves as reinforcement for the patient during the typical 6-week recovery period prior to device activation.

Clinician's Programming Interface. The device-fitting system used with the Clarion is referred to as the Clinician's Programming Interface (CPI). As shown in Fig 3, it consists of a small box with a cable that connects to the SP. This interface box is highly portable and can be connected to any standard serial port, facilitating its use with either a desk or laptop computer. Portability allows device fitting and adjustment in almost any environment: the audiology clinic, the patient's home, the child's school, or a rehabilitation facility. A portable system is especially important for young children, whose therapy and school surroundings may involve the intervention or assistance of the implant audiologist.

SPEECH PROCESSING AND DEVICE PROGRAMMING

Given the flexibility made possible with the Clarion's 8 independent output circuits, 2 speech processing strategies were offered to patients with the initial introduction of Version 1.0: the Continuous Inter-

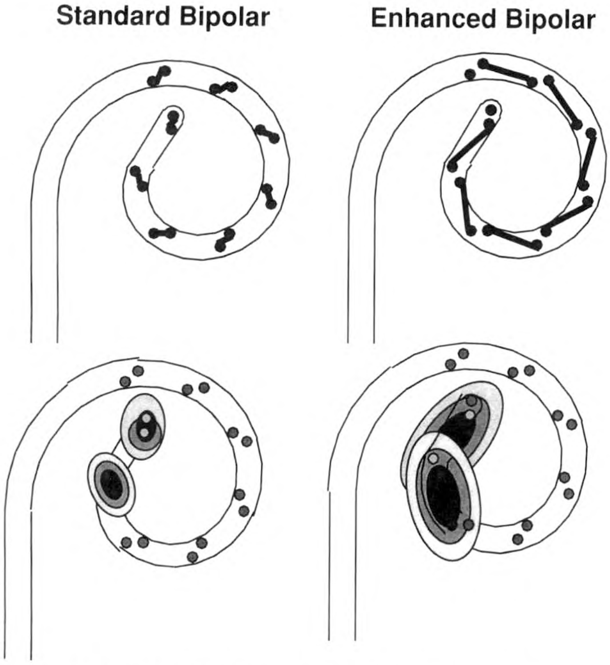


Fig 4. Standard bipolar versus enhanced bipolar electrode coupling.

leaved Sampler (CIS)[12,13] and the Compressed Analog (CA)[14,15] strategies. These processing schemes are at opposite ends of a continuum of methods for encoding the acoustic input signal into an electrical pattern capable of yielding intelligible speech. The CIS uses nonsimultaneous, pulsatile signals in monopolar mode. In contrast, the CA uses simultaneous, bipolar analog stimulation.

After some years of clinical experience, it became apparent that the vast majority of Clarion patients could not be fitted with the CA, because they were unable to achieve loudness growth with bipolar stimulation. Bipolar stimulation is preferred with simultaneous processing, because it stimulates a localized region of nerve fibers, allowing greater selectivity than the monopolar mode and counteracting the negative effects of channel interaction associated with simultaneous stimulation of the electrodes. The Clarion electrode array, because of the small surface area of its contacts and the distance between contacts (0.5 mm), was too highly selective. That is, stimulation was failing to excite a sufficient population of nerve fibers to achieve viable loudness growth. To remedy this situation and allow greater access for a larger number of patients to simultaneous processing, the bipolar coupling of the Clarion electrode was modified. In the modified coupling mode, referred to as "enhanced bipolar," the medial contact of 1 electrode pair is coupled with the lateral contact of the neighboring pair, reducing the number of bipolar channels to 7. The enhanced bipolar array increased the distance between contacts to 1.5 mm and created a wider current field, as shown in Fig 4. This change in bipolar coupling has no impact on monopolar stimulation, which retains 8 active channels. Incorporated into the Clarion's Version 1.2 ICS with either the 1.2 or S-Series processor, the enhanced bipolar electrode array provided access to the benefits of simultaneous analog stimulation (SAS) for a large number of subjects (see Osberger and Fisher, this volume, pp 74-9) and confirmed the Clarion's capacity to offer a hierarchy of processing strategies.

Speech Processing Hierarchy. Speech processing strategies can be categorized into different domains, or levels, that combine specific properties of stimulus delivery (simultaneous, nonsimultaneous, or a composite of both) and waveform presentation (analog or pulsatile). The ability to develop hybrids of various stimulus features creates a continuum of processing levels. The Clarion has designated these processing levels as S^2, S^3, and S^4.

The S^2 domain refers to nonsimultaneous pulsatile waveforms. Because most cochlear implant systems have only 1 output circuit that drives 1 electrode or channel at a time, they are restricted by their electronic design to the delivery of sequential biphasic pulses. The sequential pulse rates for strategies in this domain need to be sufficiently fast to traverse the entire electrode array within each frame while maintaining adequate temporal resolution. The speech processing strategies commonly in use today fall into the S^2 domain: SPEAK,[16] N of M,[17] CIS,[12,13] and the newer ACE,[18] promoted in the most recent Nucleus device (the N24).

The S^3 level refers to strategies that combine simultaneous and nonsimultaneous stimulation with either pulsatile waveforms or hybrid combinations of analog and pulsatile signals. Because these strategies, now under development by Advanced Bionics, require the ability to stimulate more than 1 channel at a time, the Clarion is the only system that can explore these schemes. Composite strategies in the S^3 domain should provide good temporal resolution, because signals are delivered simultaneously on 2 or more channels.

The S^4 domain refers to fully simultaneous strategies using either pulsatile or analog waveforms with active processing and stimulation occurring on all channels at the same time. Fully simultaneous processing results in the highest output rates and greatest temporal resolution of all the processing schemes. To obtain channel independence and reduce channel interactions, S^4 strategies require an electrode design and stimulation mode that produce highly focused stimulation and minimal spread of current. For these reasons, bipolar stimulation and an electrode

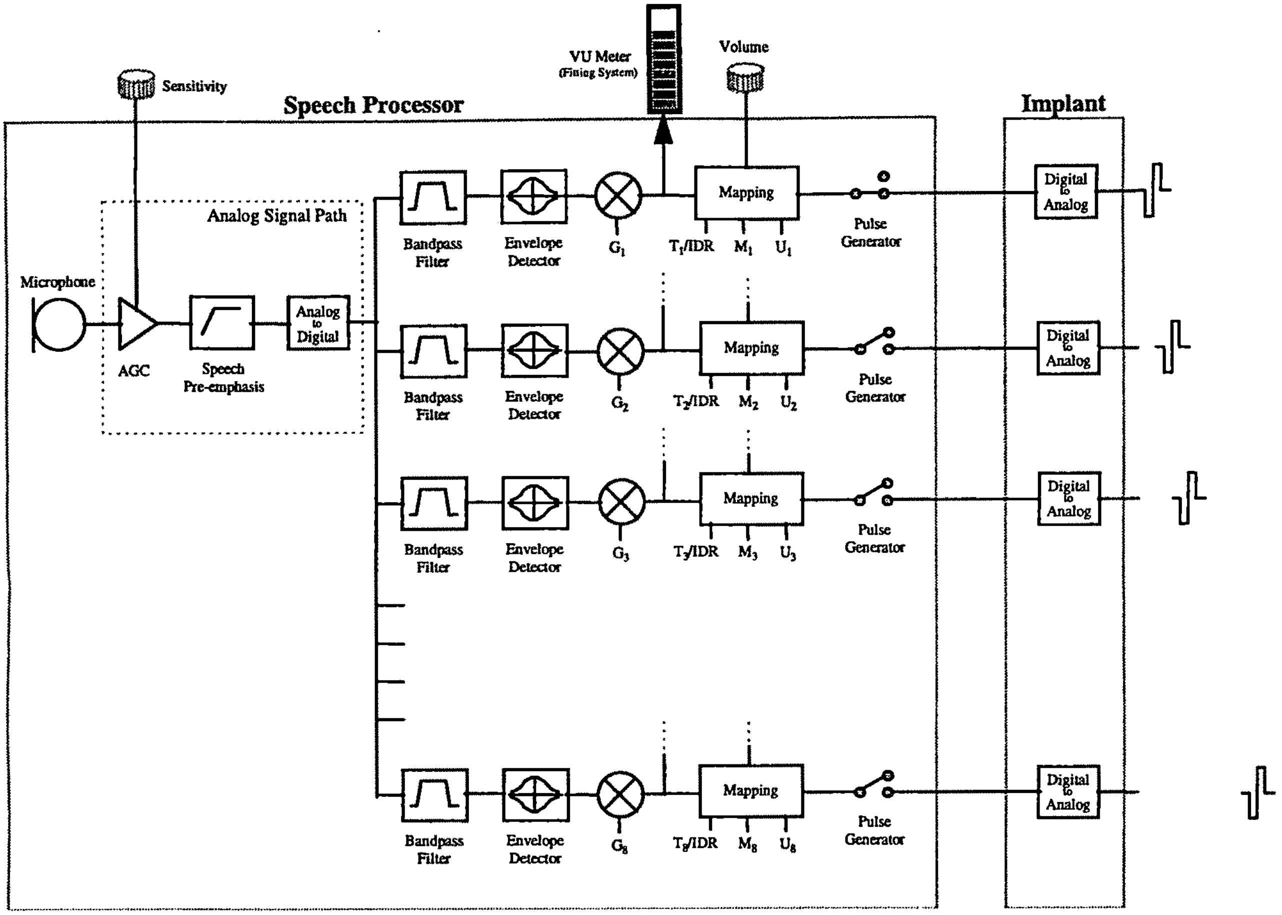


Fig 5. Block diagram of Continuous Interleaved Sampler strategy as implemented on Clarion. AGC — automatic gain control, Gn — gain for channel n, Tn — threshold level for channel n, Mn — most comfortable level for channel n, Un — uncomfortable level for channel n, IDR — input dynamic range.

that achieves modiolar proximity are favored with simultaneous processing.

Clarion Speech Processing Options. The Clarion's flexible architecture allows a variety of processing schemes that can be readily categorized into the speech processing hierarchy described above. Nevertheless, alternatives in speech processing are dependent on the software code that drives the system and on software development. It is the device-fitting software that makes alternative schemes accessible to the clinician and patient.

SCLIN. To provide patients and clinicians with speech coding options, the device fitting software must enable relatively smooth transitions from one form of stimulus to the next. While allowing audiologists easy access to alternatives and control over the ultimate schemes to be downloaded to the wearable speech processor, the software must be capable of compiling a viable program from the various elements that have been tested and measured during the device fitting session. The Clarion's device fitting software is referred to as SCLIN (Software CLINician). The SCLIN operates in a Windows™ environment. To avoid confusion and facilitate movement through the program, it has a limited number of screens that provide the clinician with a large range of options through icons, menus, and tool bars. It offers both mouse and keyboard access to all functions. The newest version of the software, referred to as SCLIN 98, is compatible with both Windows 95 and Windows 3.1 operating systems. Through the use of the Clarion's device fitting system, comprising both hardware (CPI) and software (SCLIN), users have access to all of the strategies available for clinical implementation.

Speech Processing Strategies. Since the enhanced bipolar electrode modification was introduced in 1996, 2 strategies have been available to Clarion users: CIS and SAS, a 7-channel bipolar-only modification of the CA.

The CIS strategy, developed by Blake Wilson and associates,[12,13] is a nonsimultaneous pulsatile scheme in the S^2 domain. Because the CIS requires increased speed and a greater number of channels per frame than other S^2 strategies, it conveys the full acoustic waveform without greatly compromising temporal

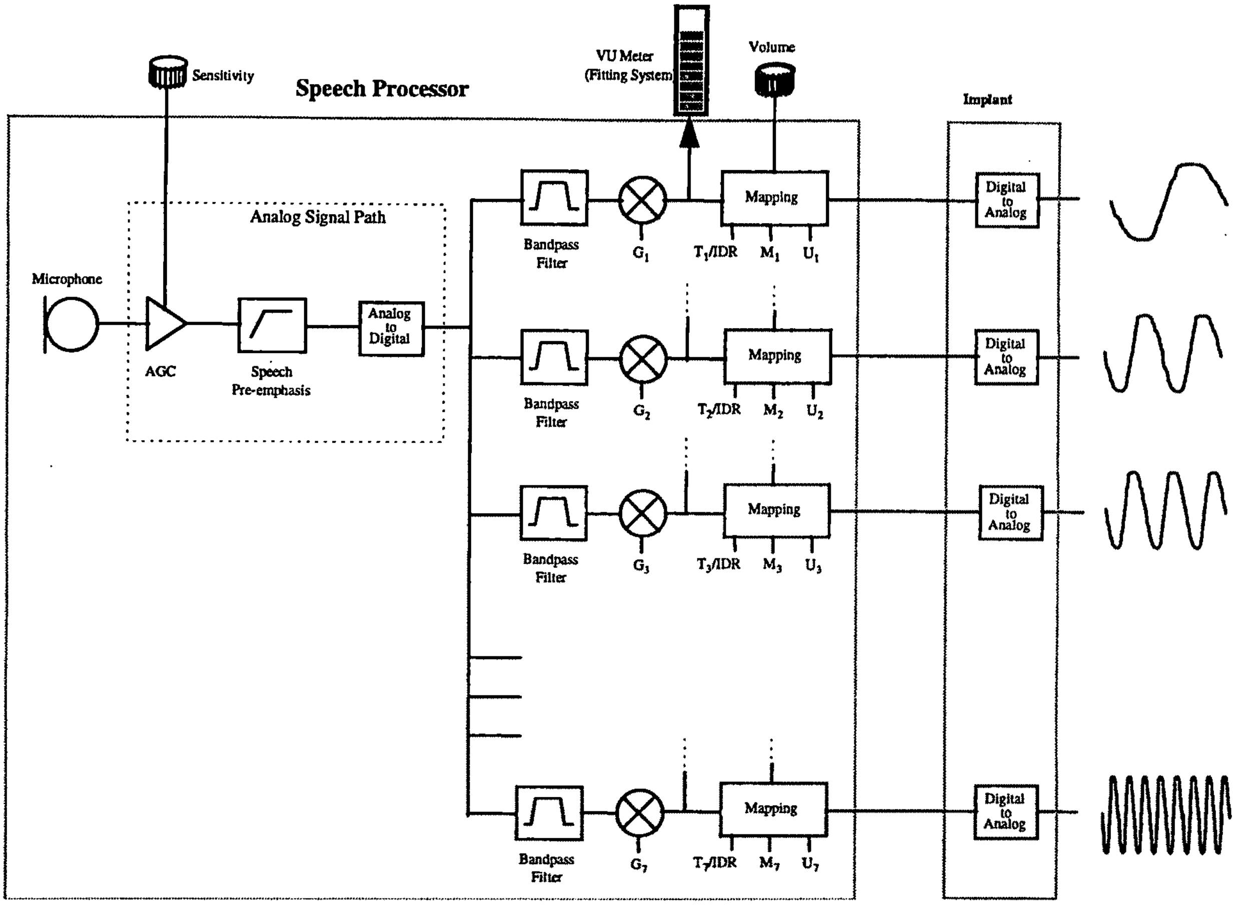


Fig 6. Block diagram of Clarion's bipolar Simultaneous Analog Stimulation strategy. See Fig 5 for abbreviations.

information. It transmits interleaved or sequential trains of balanced biphasic pulses to each channel in order to eliminate overlap across channels and minimize electrical field interactions between channels.

In the Clarion's implementation of the CIS, shown as a block diagram in Fig 5, the full spectrum of the audio input signal is divided into 8 frequency bands via a bank of bandpass filters. Each of the bandpass-filtered outputs goes through an envelope detector that extracts the sound energy within that frequency range. The energy of each frequency band is independently determined and is used to modulate the amplitude of a pulse train that is delivered to a specified electrode located in a particular region of the cochlea. In order to capture the rapid amplitude variations in speech, the CIS relies on brief pulses with minimal delays. The rate of stimulation on each channel should be at least 800 pulses per second (pps),[17] with this rate held constant during voiced and unvoiced sounds. During operation, the pulse width and the repetition rate of the signal delivered to each channel are also held constant. These parameters, as well as other adjustable features (eg, half- or full-wave rectification, electrode firing order, low-pass filtering or cutoff frequency, input dynamic range or compression, and so forth), are determined by the clinician during device fitting (see Zimmerman-Phillips and Murad, this volume, pp 17-21). The default characteristics for the Clarion's CIS include a stimulation or repetition rate of 813 pps per channel for a total update rate of 6,500 Hz with 8 active channels, a pulse width of 75 ms per phase, an apical-to-basal electrode activation sequence or firing order, and a monopolar stimulation mode.

The SAS strategy derives from the earlier CA schemes implemented in first-generation multichannel systems such as the Ineraid and UCSF/Storz devices.[14,15] Whereas those devices were true analog systems that used a vocoder approach to processing, the newer Clarion digitizes the input signal and then reconverts it to produce analog waveforms. The SAS delivers analog signals simultaneously to all the electrodes in the array in an attempt to replicate the natural properties and the normal physiological processing of sound. Because stimulation rates occur at exceptionally high speeds, simultaneous strategies are rich in detailed temporal information, but are easily confounded by the electrical field interactions or current spread produced when all the electrodes in an array are activated at once. In the Clarion, the SAS relies on its electrode to achieve modiolar proximity and focused stimulation, thereby allowing bipolar coupling that permits sufficient loudness growth while maintaining channel selectivity.

A block diagram of the SAS strategy is shown in Fig 6. As with the CIS, the full spectrum of the audio input signal is used. The incoming signal is spectrally separated into a maximum of 7 (with the enhanced bipolar electrode) frequency bands via a bank of bandpass filters. The number of frequency bands corresponds to the number of active electrode pairs or channels. In surveying the block diagrams in Figs 5 and 6, it is apparent that the analog signal path for both the CIS and SAS is identical. The input signal is digitized before entering the filter bank, and it is at the point of these bandpass-filtered outputs that the CIS and SAS diverge from one another. In the SAS, a logarithmic function is applied to each of the filtered signal outputs to compress the sound input into the electrical stimulation range. The base of the logarithm, or the degree of compression, is determined during the device-fitting session, as is the average signal level applied to each channel. After compression and adjustment of each channel's level, all of the amplitude signals are linearly scaled by a factor that is controlled by the volume dial on the patient's SP. All channels are scaled by the same factor. The processed signals are then delivered to the ICS, where they are converted to a continuous analog form by a digital-to-analog converter and finally delivered to the electrode array for simultaneous stimulation of the electrodes. The default characteristics for the Clarion's SAS strategy include an update rate of 13,000 samples per second per channel for a total update rate of 91,000 samples per second with 7 active channels and a bipolar coupling mode.

FUTURE DIRECTIONS

Safety and reliability, innovative technology, and flexibility remain key Clarion design objectives as development of the next-generation device moves forward. This device, informally referred to as the Clarion 2, will offer increased transmission speeds, enabling the exploration of new processing schemes that attempt to mimic the stochastic firing patterns of the normal auditory nerve, and high-resolution telemetry that may enable new and objective fitting techniques based on evoked potentials. Miniaturized behind-the-ear speech processors are anticipated: 1 for the current population of patients and 1 for newly implanted Clarion users.

While work on these new products is in progress, the current Clarion's capacity for speech processing options is being thoroughly mined with the development and evaluation of new strategies that exploit the Clarion's ability to transmit signals simultaneously. These strategies concern both S^3 and S^4 methods for encoding the speech signal. One such system, referred to as the Paired Pulsate Sampler (PPS™), is a CIS-like scheme in which 2 distant channels (eg, 1 and 4) are stimulated simultaneously, thus increasing the update rate almost twofold (see Zimmerman-Phillips and Murad, this volume, pp 17-21). Another strategy in the S^3 domain, called the Hybrid Analog Pulsatile processor (HAP™), is highly promising. A hybrid SAS-CIS scheme, with simultaneous analog stimulation applied in the lower frequencies and nonsimultaneous pulsate stimulation in the high, it is hoped that the HAP will preserve the fine temporal detail afforded by analog processing and the spectral information provided by CIS-type processing. The Clarion's newest processing scheme is expected to become available in the next 7 to 8 months. Called the Simultaneous Pulsatile Processor™, or the SPS, it relies on the delivery of biphasic pulses to each channel simultaneously, thereby transmitting information at an incredible speed while preserving both the spectral detail and temporal resolution of the input signal.

The Clarion's ultimate goal is to maximize patient benefit. We believe that the route to improved patient performance has just begun. With rapid advances in technology and speech processing development, we hope to enhance the quality of life and improve speech recognition for deaf and hard-of-hearing populations worldwide.

REFERENCES

1. Gantz BJ, Tyler RS, Knutson JF, et al. Evaluation of five different cochlear implant designs: audiological assessment and predictors of performance. Laryngoscope 1988;98:1100-6.

2. Cohen NL, Waltzman SB, Fisher SG. A prospective, randomized study of cochlear implants. N Engl J Med 1993;328: 233-7.

3. Abbas PJ. Electrophysiology. In: Tyler RS, ed. Cochlear implants: audiological foundations. San Diego, Calif: Singular Publishing Group, 1993:317-55.

4. Jackler RK. CT and MRI of the ear and temporal bone: current state of the art and future prospects. Am J Otol 1988; 9:232-9.

5. Wilson BS, Finley CC, Farmer JC, et al. Comparative studies of speech processing strategies for cochlear implants. Laryngoscope 1988;98:1069-77.

6. Wilson BS, Finley CC, Lawson DT, et al. Speech processors for cochlear prostheses. Proc IEEE 1988;76:1143-56.

7. Loeb G, Byers CL, Rebscher SJ, et al. Design and construction of an experimental cochlear prosthesis. Med Biol Eng Comput 1985;21:104-11.

8. Rebscher SJ. Cochlear implant design and construction. In: Gray RF, ed. Cochlear implants. San Diego, Calif: College-Hill Press, 1985:74-123.

9. Patrick JF, Clark GM. The Nucleus 22-channel cochlear implant system. Ear Hear 1991;12(suppl):3S-9S.

10. Cochlear Corporation. Nucleus 24 cochlear implant system: technology listening to your needs — specifications. February 1997.

11. Zierhofer CM, Hochmair-Desoyer IJ, Hochmair ES. Electronic design of a cochlear implant for multichannel high-rate pulsatile stimulation strategies. IEEE Trans Rehab Engin 1995;3:112-6.

12. Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. Nature 1991;352:236-8.

13. Wilson BS, Finley CC, Lawson DT, Wolford RD, Zerbi M. Design and evaluation of a continuous interleaved sampling (CIS) processing strategy for multichannel cochlear implants. J Rehabil Res Dev 1993;30:110-6.

14. Eddington DK. Speech discrimination in deaf subjects with cochlear implants. J Acoust Soc Am 1980;68:885-91.

15. Schindler RS, Kessler DK, Rebscher SJ, Yanda JL, Jackler RK. The UCSF/Storz multichannel cochlear implant: patient results. Laryngoscope 1986;96:597-603.

16. McKay CM, McDermott HJ. Perceptual performance of subjects with cochlear implants using the Spectral Maxima Sound Processor (SMSP) and the Mini Speech Processor (MSP). Ear Hear 1993;14:350-67.

17. Lawson DT, Wilson BS, Zerbi M, et al. Speech processors for auditory prostheses. NIH Contract N01-DC-5-2103, Third Quarterly Progress Report, February 1, 1996, through April 30, 1996.

18. Staller SJ. Clinical trials of the Nucleus 24 in adults and children. Presented at the 10th Annual Convention of the American Academy of Audiology, Los Angeles, Calif, April 2-5, 1998.

Ann Otol Rhinol Laryngol 108:1999

PROGRAMMING FEATURES OF THE CLARION® MULTI-STRATEGY™ COCHLEAR IMPLANT

SUSAN ZIMMERMAN-PHILLIPS, MS CAROL MURAD, MSC
SYLMAR, CALIFORNIA

Because patient performance with multichannel cochlear implants varies widely, cochlear implant systems must address the diverse needs of patients during the postoperative fitting of the external equipment. This paper describes the processing strategies available with the CLARION® Multi-Strategy™ Cochlear Implant and the different programming features available for optimization of these speech processing strategies. In addition, preliminary data are presented about the frequency of use of various fitting parameters with adult Simultaneous Analog Stimulation (SAS) and Continuous Interleaved Sampler (CIS) patients and pediatric CIS users. The data reveal that many of the programming features available to the clinician are useful with both the adult and pediatric populations and across strategies. The flexibility of both processing strategies and the programming options clearly contribute to the optimization of patient device fittings. Optimized device fittings, in turn, maximize patient performance.

KEY WORDS — cochlear implant, device programming, psychophysical measurements, software.

INTRODUCTION

To provide cochlear implant patients with an optimal device fitting, a greater number of speech processing options and increased sophistication in programming software and device fitting techniques have become available in recent years. In addition, the worldwide trend to implant children at increasingly younger ages has introduced the challenge of programming cochlear implant systems on the basis of minimal psychophysical information.

This paper describes the flexibility of the CLARION® Multi-Strategy™ Cochlear Implant with regard to speech processing strategies and the programming options available to the clinician for fitting optimization. Flexibility is required to meet the demands that each patient brings to the fitting arena. The Clarion offers a hierarchy of processing capabilities. Its multiple output circuits, high transmission rate, fast sampling speed, and modiolar-hugging electrode design make simultaneous stimulation a viable option — a processing scheme that is unique among current cochlear implant systems. Recent studies suggest that the availability of processing options may result in improved group performance scores, indicating that individual subjects achieve higher levels of speech recognition when fitted with a strategy that is customized to suit their needs.

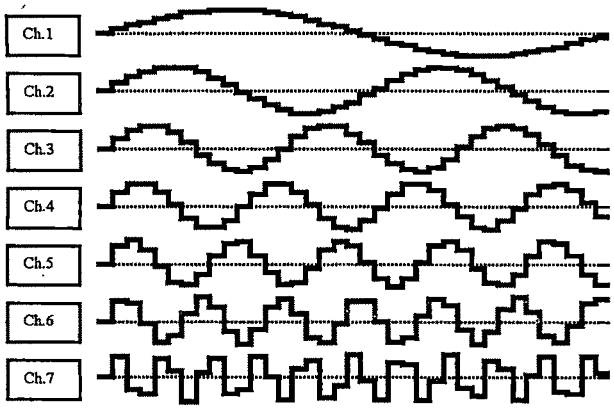


Fig 1. Pattern of stimulation across channels used in Simultaneous Analog Stimulation (SAS) programming strategy.

SPEECH PROCESSING OPTIONS

The Clarion currently offers 2 radically different speech processing strategies. Adult patients are routinely fitted with both strategies during the initial programming session. Simultaneous Analog Stimulation (SAS) is a fully simultaneous strategy that digitally reconstructs the analog waveform (Fig 1). When 7 channels are operating simultaneously, it samples the input signal at a rate of 91,000 samples per second. The Continuous Interleaved Sampler (CIS) is a nonsimultaneous strategy that delivers pulsatile stimulation sequentially across the 8 channels at a rate of 6,500 pulses per second (Fig 2). A partially simultaneous strategy, referred to as the Paired Pulsatile Sampler (PPS), also has become available recently. Similar to CIS, PPS is a pulsatile strategy that takes advantage of the Clarion's unique ability to stimulate 2 channels concurrently, increasing the overall update rate to 13,300 pulses per second (Fig 3).

Because the Clarion offers multiple speech processing schemes, fitting the device has 2 primary objectives: 1) to determine the most beneficial speech cod-

---

From Advanced Bionics Corporation, Sylmar, California.
CORRESPONDENCE — Susan Zimmerman-Phillips, MS, Advanced Bionics Corporation, 12740 San Fernando Rd, Sylmar, CA 91342.

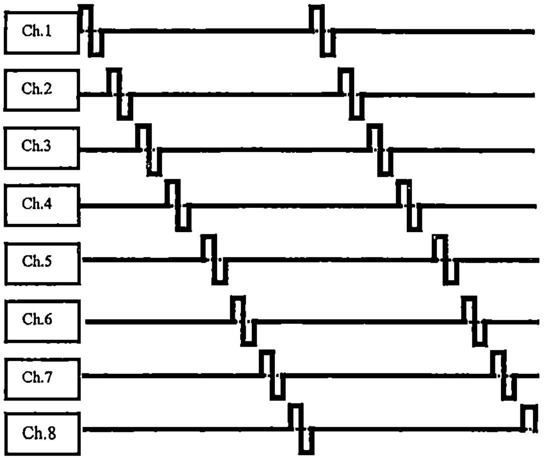


Fig 2. Pattern of pulsatile stimulation across channels used in Continuous Interleaved Sampler (CIS) programming strategy.

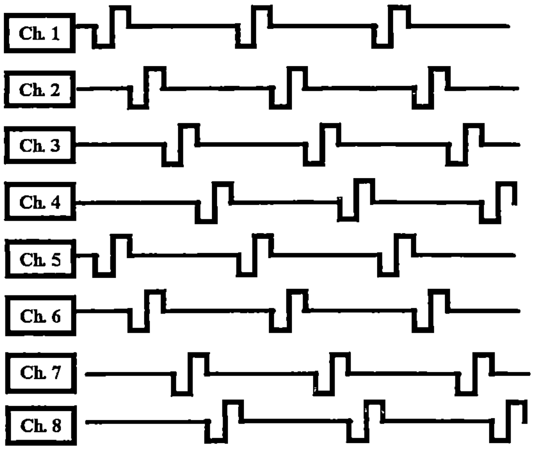


Fig 3. Pattern of pulsatile stimulation across channels used in Paired Pulsatile Sampler (PPS) programming strategy.

ing strategy for the individual patient and 2) to provide the most effective settings for the selected processing strategy. Adults are fitted routinely with both SAS and CIS, allowing them listening experience with both schemes. While taking the subjective response of patients into account, the ultimate decision regarding the appropriate processing strategy for a given patient is in the hands of the implant audiologist. Preliminary results suggest that when given a choice between SAS and CIS, adults generally show a strong preference for one or the other within the first few weeks of device use. Early results also indicate that overall performance scores improve when adults have access to SAS (see Osberger and Fisher, this volume, pp 74-9).

DEVICE FITTING SYSTEM

The Clarion's fitting system consists of a Windows™-based software program called SCLIN (Software CLINician). SCLIN 98, the most recent version of the fitting software, is compatible with both Windows 95 and 3.1 operating systems and allows the audiologist to fit patients with all of the available strategies. With each speech processing strategy, the clinician is able to manipulate stimulus parameters to meet individual patient needs. The ability to change these parameters increases the likelihood of effectively addressing difficult fitting issues via programming. In turn, this increases the capacity to optimize device fitting for each individual patient.

Because the speech processor has the capacity to store 3 different programs, access to different strategies and different adjustments within a strategy allow the patient to evaluate different programs in various listening environments. Many patients have programs fitted for specific situations they encounter in their daily lives, such as telephone use, listening to music, or conversing in competing background noise.

PROGRAMMING FEATURES

The information presented here includes brief descriptions of programming features available with the Clarion. The utility of these features in difficult-to-fit patient populations is discussed, and preliminary data on the frequency with which the clinician makes use of these features are presented.

Interpolation of Psychophysical Measures. As with all other cochlear implant systems, a minimum amount of psychophysical information must be obtained in order to compile a viable program. Threshold and comfortable loudness levels for each electrode are the first measurements made and are required for program compilation. For monopolar pulsatile stimulation, the Clarion offers an interpolate feature that uses measured threshold (T) and most comfortable loudness (M) values from 1 or 2 channels to estimate the T and M levels for the remaining channels. The software interpolates the levels by fitting a straight line between the measured values. This feature is based on the relative uniformity of loudness levels from channel to channel among patients fitted with the monopolar pulsatile CIS strategy (see Osberger and Fisher, this volume, pp 74-9).

The interpolate feature is used primarily with pediatric and difficult-to-fit patients. It is particularly helpful early in the fitting process, when patients are unable to scale loudness. In these cases, the clinician can make use of this feature to create a full program when psychophysical data may only be available for 1 or 2 channels or when time is at a premium, as in the case of young children with short attention spans.

Variable Pulse Width. With CIS or PPS, the clinician can select pulse widths varying from 75 to 300 microseconds on each channel. In the software, this parameter is accessible when establishing T and M levels, because it is during these measurements that the clinician is most often alerted to the need to increase pulse width, such as in the case of insufficient loudness growth on a given channel. However, the audiologist must be aware of the inverse relationship between pulse width and repetition rate. When pulse width is increased, repetition rate is decreased, and this effect might influence the patient's perception. In attempting to provide patients with an optimal fitting, trade-offs such as these must be evaluated carefully.

Electrode Coupling. The default stimulation mode for the SAS strategy is bipolar; the medial and lateral contacts of each electrode pair are coupled. This stimulation mode maximizes channel selectivity during simultaneous stimulation, when channel interactions are most likely to occur. Monopolar stimulation, with the medial contacts as the active electrodes, is the CIS default mode. The software allows the clinician to program any combination of the 16 electrode contacts. Use of the medial electrodes is most common because they are closest to the spiral ganglion cells. However, a lateral electrode contact may be used if its medial counterpart is not functioning optimally. A patient can use all medial, all lateral, or a combination of medial and lateral electrode contacts, depending on his or her specific needs.

Live-Voice Speech Adjustments. One of the most useful features of SCLIN is the ability to use live-voice speech to assess parameter settings. Adjustments of loudness levels, Input Dynamic Range (IDR), frequency emphasis, and the speech processor volume dial can all be made with live-voice input. Thus, the patient can evaluate the influence of programming adjustments on the quality and clarity of speech. Moreover, speech stimuli are more meaningful to children than tones. The ability to make parametric adjustments while presenting live-voice speech allows the audiologist to make program changes without disruption, resulting in a flowing, dynamic fitting process.

SCLIN allows the clinician to use live-voice speech to adjust psychophysical measurements obtained with nonspeech stimuli. The audiologist can increase or decrease loudness levels globally while speaking to the patient to set a "speech M," or comfort level for speech. SCLIN also incorporates a speech display with individual channel voltage-unit (VU) meters. This display provides a real-time representation of the relative amplitude of the signal spectrum across channels, providing the clinician with visualization of the amount of speech energy present in each channel.

The majority of implant users report increased difficulties in understanding speech in the presence of background noise. Manipulation of the IDR globally maps higher levels of sound onto the patient's electrical dynamic range. This adjustment often results in better communication in the presence of competing background noise, because low-level noise is excluded from the patient's program. The clinician can manipulate the IDR level and assess its effect with live-voice speech.

Five frequency shaping templates are available with SCLIN. The audiologist has the ability to adjust the gain on the frequency bands of the incoming signal by using these templates. Individual channel gain adjustments can also be made to create a custom frequency response based on an individual patient's needs.

The speech processor has both a volume dial and a sensitivity control. (The sensitivity control adjusts the sensitivity of the microphone on the headpiece.) The volume dial is programmable and can be used to specify values for the upper limit of stimulation (upper level of comfortable loudness; ULCL) and lower limit of stimulation (lower comfort level; LCL). Typically, the ULCL, LCL, and threshold levels (T) are based on individual psychophysical measurements. However, in some cases, the clinician may use the programmable volume dial to set the ULCL and LCL values. For example, the clinician may set the LCL at a point above threshold so that pediatric patients will still hear sound even if they turn the volume dial all the way down. Limiting the "play" of the volume dial by specifying the ULCL or LCL may be useful when the dial may be manipulated unintentionally, for example, by a young child or a physically active adult.

Special Patient Populations. Patients once considered unsuitable for implantation are now being implanted routinely. For example, implanting individuals with ossified or malformed cochleas is not uncommon. Adults who are congenitally deaf or who have experienced a long duration of deafness are routinely receiving cochlear implants. Pediatric implant users are increasingly younger. Expanding the number of viable surgical candidates increases the likelihood of encountering unique fitting requirements, and thereby increases the need for a flexible programming system.

Variable pulse widths are useful for patients who experience difficulty achieving loudness growth on 1 or more channels. This situation is not uncommon in implant recipients with ossified or malformed cochleas or in patients with a long duration of deaf-

TABLE 1. PERCENTAGE OF INTERPOLATED VALUES FOR THRESHOLD AND MCL LEVELS AT INITIAL STIMULATION AND THREE-MONTH POSTOPERATIVE EVALUATION FOR PEDIATRIC PATIENTS

Channel No.	*Initial Stimulation (%)*		*Three-Month Evaluation (%)*	
	Threshold	*MCL*	*Threshold*	*MCL*
1	2	20	0	0
2	9	30	0	0
3	14	24	14	0
4	25	35	14	0
5	26	29	31	3
6	25	32	31	3
7	22	29	22	8
8	3	18	6	3

MCL — most comfortable loudness.

ness prior to implantation. Setting the maximum stimulation levels (clipping levels) on individual channels is particularly useful in instances of nonauditory response, such as facial nerve, vestibular, or tactile stimulation, and can prevent eliminating a channel from the program. The option of using a medial or lateral contact on the same electrode pair also can prevent elimination of a channel. In situations of nonauditory stimulation, narrow dynamic range, or an aberrant electrode, use of a mixed coupling mode allows the audiologist to "program around the problem."

Fitting a young child optimally is a challenge to clinicians.[1] Limited linguistic skills, short attention span, and inexperience with audition all contribute to this programming challenge. SCLIN features that are particularly useful with the pediatric population include interpolation of psychophysical values, setting speech M, access to multiple programs in the speech processor, and objective measurements. Valuable hardware features include programmable alarms for low battery status or headpiece disconnection and a speech LED indicator (see Kessler, this volume, pp 8-16).

USE OF PROGRAMMING FEATURES

The following section summarizes the frequency with which SCLIN programming features were used with adults (n = 129) and children (n = 39) implanted with the S-Series electrode (enhanced bipolar electrode). The adult patients used either CIS (n = 69) or SAS (n = 60), whereas all children used the CIS strategy. Patients used either the 1.2 or S-Series speech processor. SCLIN data were collected at the initial fitting and 3 months after the initial device fitting.

Interpolate Feature. The frequency of interpolated T and M values in pediatric fittings is summarized in Table 1. The interpolate feature was seldom used to program threshold values on the most apical channel (channel 1) or the basal channels (channels 7 and 8). The values on the remaining channels were interpolated about 25% of the time. A similar pattern was observed for M values, with the use of interpolated values slightly higher than for T values. This pattern is not unexpected, since most implant recipients initially have difficulty in loudness scaling and in establishing a comfort level. At the 3-month test interval, most T and M values were measured rather than interpolated.

TABLE 2. PERCENTAGE OF PATIENTS WITH VOLUME DIAL PROGRAMMED FOR ULCL AND LCL AT INITIAL STIMULATION AND THREE-MONTH POSTOPERATIVE EVALUATION

Program Volume Dial	*Initial Stimulation (%)*		*Three-Month Evaluation (%)*	
	ULCL	*LCL*	*ULCL*	*LCL*
Adult	79	15	60	25
Pediatric	9	5	17	17

ULCL — upper level of comfortable loudness, LCL — lower comfort level.

Programmable Volume Dial. The percentage of patients for whom the volume dial was programmed are shown in Table 2. At initial fitting, more than two thirds of the patients had their volume dial programmed with the upper limit of loudness (ULCL). This number decreased to 60% at the 3-month evaluation. The LCL was programmed to a far lesser degree than the ULCL. The programmable volume dial was seldom used with pediatric patients. This is most likely due to the large changes in loudness growth that typically occur during early phases of implant use in young children. If upper and lower limits are not set, a global increase in loudness can be achieved with the clockwise rotation of the volume dial. On the basis of observations and the child's response to sound, parents and teachers can make these changes and adjust loudness levels without visiting the implant center.

Input Dynamic Range. Table 3 illustrates adjustments of the IDR. In adults, the IDR was manipulated from the default setting more than half of the time at both the initial stimulation and the 3-month evaluation. This feature was also used with children frequently at initial stimulation, with an increased use at the 3-month fitting.

Frequency Shaping Templates. The use of the Frequency Shaping templates is detailed in Table 4. The majority of the frequency response curves were maintained at the default setting (ie, flat response from 250 to 6,800 Hz) in both the adult and pediatric populations. This feature typically is manipulated to enhance overall sound quality and is based primarily on patient feedback. Its relatively limited use with

TABLE 3. PERCENTAGE OF PATIENTS WITH INPUT DYNAMIC RANGE SETTING MANIPULATED AT INITIAL STIMULATION AND THREE-MONTH POSTOPERATIVE EVALUATION

Input Dynamic Range	*Initial Stimulation (%)*	*Three-Month Evaluation (%)*
CIS, adults	61	52
CIS, pediatric	66	81
SAS, adults	42	53

CIS — Continuous Interleaved Sampler, SAS — Simultaneous Analog Stimulation.

TABLE 4. PERCENTAGE OF PATIENTS USING SPECIFIED FREQUENCY-SHAPING TEMPLATE AT INITIAL STIMULATION AND THREE-MONTH POSTOPERATIVE EVALUATION

Frequency Shaping	*Initial Stimulation (%)*	*Three-Month Evaluation (%)*
Adult (CIS users)		
Flat (default value)	47	50
Middle-frequency emphasis	30	26
High-frequency emphasis	13	17
Adult (SAS users)		
Flat (default value)	62	39
Middle-frequency emphasis	20	20
High-frequency emphasis	12	33
Pediatric (CIS users)		
Flat (default value)	88	92
Middle-frequency emphasis	6	6
High-frequency emphasis	6	0
Low-frequency emphasis	0	6

children may reflect difficulty in "fine-tuning" or "tweaking" the program in young children, who are unable to provide feedback. The second most commonly used template was middle-frequency emphasis, followed by high-frequency emphasis. This pattern did not change substantially from the initial fitting to the 3-month evaluation for CIS users. However, this parameter was manipulated over time with the SAS strategy. This finding may reflect increasing clinician experience in programming SAS, rather than a change in patients' perception of sound quality. That is, by the 3-month test interval, audiologists may have gained greater confidence in addressing patient feedback via programming changes. The preference for high-frequency–emphasis programs may reflect the attempt to address the common descriptions of "hollow" or "low-frequency" sound quality frequently reported by SAS users.

SUMMARY

In summary, SCLIN for Windows™ provides the audiologist with a large number of programming options. Programming flexibility is available for all patients, especially those who are difficult to fit. Software and fitting flexibility is becoming increasingly important as the candidacy criteria expand and more programming challenges are encountered. The data in Tables 1-4 indicate that clinicians frequently use these features when fitting their Clarion patients. These data provide insight into the parameter adjustments that implant audiologists regard as important and useful for different patient populations and the application of different speech processing strategies.

REFERENCE

1. Firszt JB, Reeder RM. Cochlear implants and children: device programming and considerations for young children. Semin Hear 1996;17:337-50.

Ann Otol Rhinol Laryngol 108:1999

CLINICAL RESULTS OF THE CLARION® MAGNETLESS COCHLEAR IMPLANT

BENNO P. WEBER, MD, PHD
HANNOVER, GERMANY
JÜRGEN NEUBURGER, MD
HANNOVER, GERMANY
JENNY E. GOLDRING, MSC
HANNOVER, GERMANY
THOMAS SANTOGROSSI, BENG
SYLMAR, CALIFORNIA
HERBERT KOESTLER, PHD
HANNOVER, GERMANY
ROLF D. BATTMER, PHD
HANNOVER, GERMANY
THOMAS LENARZ, MD, PHD
HANNOVER, GERMANY

This paper reports initial results for the CLARION® Multi-Strategy™ Cochlear Implant, presently under investigational study in Europe. A magnetless implantable cochlear stimulator (ICS) with an ear-mold–supported headpiece was designed in response to an increasing demand for a magnetic resonance imaging (MRI)–compatible cochlear implant. Surgical technique, accompanying magnetless headpiece, and MRI compatibility were evaluated in 11 deaf patients (ages 6 to 62 years) who were implanted with a magnetless Clarion implant. Because of the headset mechanics, the ICS was implanted closer behind the ear than a magnet-containing ICS. The ICS-MRI compatibility was investigated with 1.5- and 0.3-T MRI. Results showed that the surgery was relatively safe and easy to learn. The headset was stable and reliable. The MRI compatibility tests indicate that the ICS poses no contraindication for patients needing MRI. Overall, the results suggest that the Clarion magnetless cochlear implant is relatively safe and easy to implant, is MRI-compatible, and functions well with the ear-mold–supported headpiece.

KEY WORDS — cochlea, cochlear implant, magnetic resonance imaging.

OBJECTIVE

The purpose of this paper is to report initial clinical results for the CLARION® Multi-Strategy™ Cochlear Implant, presently under investigational study in Europe. The objectives were to evaluate the accuracy of the surgical implant placement, the function of the corresponding magnetless headpiece, and magnetic resonance imaging (MRI) compatibility.

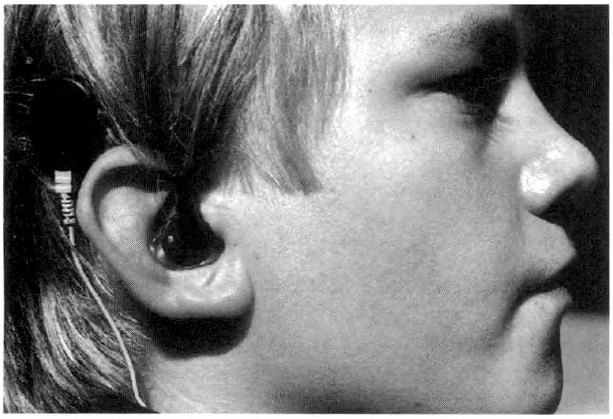
BACKGROUND

Cochlear implants are becoming more widespread as a means of restoring hearing sensation by electrically stimulating the auditory nerve in individuals who have bilateral sensorineural deafness. The Clarion cochlear implant consists of both internal and external components. The internal components, surgically implanted under the skin behind the ear and in the cochlea, include the implantable cochlear stimulator (ICS) and the intracochlear electrode array. The external components include a speech processor, a headpiece, and a cable. Both the ICS and headpiece contain a magnet, in order to align to one another. Unfortunately, this internal magnet poses problems for cochlear implant patients needing MRI.[1-4] Although recent studies have suggested MRI poses no major risk to many cochlear implant patients,[5,6] image distortion did occur. In contrast, other recent studies have found significant torque effects on the implant and demagnetization with the standard 1.5-T MRI.[7,8]

Consequently, to allow safe and accurate MRI for Clarion cochlear implant patients, a magnetless implant was designed with a special magnetless headpiece. The magnetless ICS is exactly the same as the Clarion 1.2 ICS (Advanced Bionics, Sylmar, Calif) except that the magnet was removed. The special magnetless headpiece (Hannover headset by Bruckhoff and Partners, Hannover, Germany) was based on a modern hearing aid design (DEAMO) in which the antenna enclosure is held in place by an ear-mold, connected by a padded flexible wire (see Figure). The ear-mold (which snaps onto the headpiece) is open to the air to allow a more comfortable fit. In addition, the microphone is placed close to the hearing canal within the concha to better simulate a natural listening situation. The comfortable and attractive hearing aid design is preferred by many patients over the magnet-containing headpiece that fits over the ear. The headpiece can be used by patients who already use the regular magnetic Clarion ICS.

From the Departments of Otolaryngology (Weber, Neuburger, Goldring, Battmer, Lenarz) and Neuroradiology (Koestler), Medizinische Hochschule Hannover, Hannover, and Advanced Bionics GmbH, Merzig (Goldring), Germany, and Advanced Bionics Corporation, Sylmar, California (Santogrossi).

CORRESPONDENCE — Benno P. Weber, MD, PhD, Dept of Otolaryngology, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.



Magnetless headpiece worn by child. Components include antenna enclosure, padded flexible wire, and ear-mold. Microphone is positioned near ear-mold.

PATIENTS

All patients were implanted and fitted with the magnetless device at the cochlear implant center of the Medical University of Hannover (Medizinische Hochschule Hannover; MHH). The results will be presented for the first 11 patients (10 male, 1 female) at MHH. The patient demographics are listed in the Table. All patients were German-speaking (with the exception of 1 Italian), with a postlingual onset of hearing loss (with the exception of 2 prelingually deaf children). Children under the age of 4 were excluded from this first investigation because of concerns about headpiece stability. Additional exclusion criteria included eczema, pathologic deformity of the external auditory canal, a case history of difficulty wearing ear-molds, or an absent pinna. Preoperative computed tomography (CT) scans showed that none of the patients had cochlear obliterations.

All patients visited the Bruckhoff and Partners hearing aid dealer preoperatively to ensure that the magnetless headpiece could be properly fitted. The actual ear-mold fitting took place 4 to 6 weeks after implantation, once the wound had healed and the ear canal shape had stabilized. The reasons for using the magnetless implant and/or magnetless headpiece for each of the patients are listed in the Table. Typically, they were either an anticipated future need for MRI, a preference for better microphone position, or aesthetics. Preoperatively, the patients were informed that the magnetless implant and headpiece were not commercially available, but were under investigation. Ethical approval was obtained from the ethics committee of MHH, and approval for the extension of this study for patients 2 years and older has been received from the Freiburg Ethics Committee International.

PATIENT DEMOGRAPHICS AS OF JANUARY 30, 1998

Subject	*Age at Implantation (y)*	*Cause of Deafness*	*Motivation for Magnetless Device*	*Time With Implant (mo)*
1	30	Meningitis	Aesthetics	27
2	11	Familial or congenital	MRI compatibility	19
3	52	Trauma	Microphone position	11
4	8	Congenital	MRI compatibility	10
5	33	Rubeola	Aesthetics	10
6	47	Familial	Microphone position	10
7	35	Acute hearing loss	MRI compatibility	9
8	28	Acute hearing loss	MRI compatibility	8
9	32	Congenital	Aesthetics	6
10	6	Coma and toxicity	MRI compatibility	5
11	62	Familial	Aesthetics and microphone position	1.5

MRI — magnetic resonance imaging.

METHODS

Surgical Technique. To facilitate fitting of the ear-mold–supported headpiece, the ICS was implanted slightly closer behind the ear than a standard ICS. The best ICS location was determined preoperatively with a plastic mock-up. In general, the edge of the ICS was positioned far enough from the posterior edge of the pinna to leave space for the earpiece of eyeglasses. Compared to the standard Clarion 1.2 ICS location, the magnetless ICS was rotated about 70° clockwise for the right ear and 70° counterclockwise for the left ear, with the fantail pointing inferior and slightly posterior, with enough freedom left for the fantail.

To ensure that the bone was thick enough to accommodate the ICS, a CT scan was taken of the first patients with a plastic mock-up ICS taped to the approximate planned position behind the ear. After the position was determined, the ICS location was traced with a permanent marker on the skin. Just prior to incision, a transcutaneous mode of marking was used to mark the relevant bone region, by means of a metal marking template with 2 marking holes. The most noninvasive marking technique involved injecting methylene blue through the 2 marking holes. However, a more accurate method was to use screws or to drill 2 small holes in the bone of the skull.

Because of the behind-the-ear (BTE) location of the headpiece, the BTE incision adopted by some clinics for cochlear implantation could not be used.

A Hannover incision was made, with the incision line 1.5 to 2 cm from the ICS edge. After the skin flap was raised, the ICS location on the bone was identified from the 2 blue marks, holes, or screws, together with a thin metal ICS mock-up (with 2 corresponding holes). Sometimes, the position needed to be adjusted slightly. The ICS position was traced on the skull, and surgery proceeded as in a standard Clarion 1.2 implantation.

Headpiece. Mechanical, physical, and medical aspects of the headpiece were evaluated by patient interview, speech therapist or engineer observation, and medical checkup. Because there was no magnetic attraction between the ICS and the headpiece, a misalignment and consequent loss of information transmission could have occurred between the magnetless headpiece and the skin (ie, greater space between the ICS and headpiece). For this reason, there were concerns regarding stability, lock power, and the possible need for greater radio frequency (RF) energy. The lock power is the ability of the ICS and headpiece to communicate across the skin. The RF energy is the voltage needed to transmit the signal. The greater the RF power required, the greater the battery consumption. Thus, the mechanical concerns addressed were ease of headpiece and speech processor fitting, battery life, and RF power. The physical issues evaluated were stability, ear-mold position, and microphone position. In addition, the medical condition of the patient was noted to ensure the headpiece and ear-mold did not cause any allergies, itching, bruising, pressure points, or other side effects.

MRI Compatibility. The compatibility of the magnetless ICS was tested with 1.5-T tunnel design MRI and 0.3-T open air design MRI. The compatibility test protocol was the one used for MRI compatibility testing with the Clarion 1.2 implant.[8] The concerns, as underlined by Chou et al,[9] were force exerted on the implant by the magnetic field; heat generation due to absorption of RF energy; unintentional current output due to the electromagnetic field; implant damage due to RF exposure; and distortion, a darkening of the MRI image due to the implant. Additionally, and perhaps most important, the torque (force causing rotation) exerted on the implant by the static magnetic field was tested. A phantom head was used for all tests except the image distortion tests, in which a human head was used.

RESULTS

Surgical. There were no surgical complications in the 11 patients. The preoperative CT scan with a plastic dummy was deemed useful for identifying bone thickness. The surgical method of implanting the ICS closer behind the ear was both relatively safe and easy to learn. The mock-up ICS and drilling template with marking holes functioned well in determining the proper BTE location. Achieving the optimal position is important to avoid moving the ear. To ensure that the ICS bone bed was truly in the same location as marked on the skin preoperatively, transcutaneous marking was necessary. All 3 methods (dye, screws, drilling) worked well, although the risk of infection is theoretically greater with drilling, and the risk of improper marking is slightly higher with the dye. Due to the various sizes and anatomy of the patients, the BTE placement was slightly different for each person. In children, it was important to take into account future growth, so the ICS was implanted slightly more superiorly than for an adult. At the request of some patients, the ICS was implanted slightly closer to or farther from the pinna.

Headpiece. Postoperative fitting of the headpiece and speech processor were successful and exceeded expectations. For all ages, the headpiece was quite stable and, despite the differences in ICS locations, the headpiece could be easily fitted. The padded flexible wire between the ear-mold and antenna enclosure could be adjusted and could tolerate about 20 g of tractive force. Since the start of this study, a magnetless headpiece measuring mock-up has been made. This mock-up allows the clinician to estimate where the antenna enclosure will sit on the skin and allows the clinic to measure the length of the flexible wire needed. Because the headpiece comes with a variety of wire lengths between the ear-mold and headpiece, the headpiece can be fitted individually to each patient.

The engineers fitting the speech processor reported that the headpiece made good contact with the ICS. It should be noted, however, that the magnetless headpiece required a slight increase in lock (voltage) power compared to the standard headpiece (about a 15% to 20% increase), and the battery life was sometimes up to 1 hour shorter. The signal link between the headpiece and the ICS was reliable, even though the gap between the skin and the headpiece ranged between 0 and 3 mm. The distance that the headpiece could be moved before losing the RF link ranged between 2 and 6 mm, depending on the thickness of the underlying skin.

All patients, when properly fitted, were satisfied with their ear-mold. Four patients reported that the ear-mold was uncomfortable at first because of pressure against the skin of the concha. This problem was quickly and easily repaired by shaving small pieces off the ear-mold until the fit was comfortable. Most of the patients are very active, and all are able to wear their headpieces while participating in sports or other activities. All patients also were satisfied with the position of the microphone, reporting that they could hear well, especially from the side and some from the front. When they were using the telephone, the microphone position was ideal. When asked, all patients reported that they were very satisfied with the function and attractiveness of the magnetless headpiece. The children were very happy with the appearance of the headpiece, wishing only for other colors.

None of the patients experienced allergic reactions to the headpiece. There were no negative medical side effects from the headpiece, except for minor redness or irritation at the concha if the ear-mold was not properly fitted the first time.

MRI Compatibility. The results of the compatibility study were encouraging. In both the 1.5- and 0.3-T units, the ICS showed no significant torque and the force was less than about 0.01 newtons. There was no significant increase in implant temperature during scanning, no unintentional current output, and no implant damage. When the ICS was taped to a human head and scanned with a single-shot fast spin echo in the 1.5-T unit, there was minimal artifact, which consisted of shading with a radius of up to about 20 mm around the implant. With a fast spin echo, the resolution was better, but caused slight shading with a radius of up to about 30 mm around the implant. In the 0.3-T imager, the implant was strapped to a phantom head. With a spin echo sequence, there was a blacking effect with a radius of up to 45 mm in the area around the implant.

DISCUSSION

The MRI compatibility is of utmost importance to cochlear implant candidates because of the increasing use of this nonirradiating method of diagnostic imaging. An MRI-compatible cochlear implant has been developed by Cochlear Corporation (Englewood, Colo), but the device is a magnet-containing implant in which the magnet can be removed after implantation. To remove the magnet, however, an additional operation is required. The development of the Clarion magnetless implant with its accompanying magnetless headpiece eliminates the need for additional surgery.

The surgical technique with the magnetless implant differed only slightly from the standard Clarion procedure. The main difference was the location of the ICS. To allow the best fitting of the ear-mold–supported headpiece, implant placement needed to be close behind the ear, but far enough from the edge of the pinna to allow space for eyeglasses. It should be noted, however, that because the wire length between the ear-mold and the antenna enclosure can be adjusted, the headpiece can accommodate a variety of ICS positions, with some limitations. A preoperative CT scan can be performed to check bone thickness, and to control placement most accurately, use of an ICS mock-up and drilling template with guiding holes for marking the intended bone region is advised. The surgical procedures proved to be relatively safe and easy to learn. At present, the Clarion cochlear implant uses a body-worn speech processor. With the expected introduction of a BTE speech processor, there were some concerns about whether the magnetless implant would allow enough room for a BTE processor. We now believe that integration of a BTE processor and a magnetless headpiece with the magnetless implant is feasible.

Physically and mechanically, the magnetless headpiece functioned well. When the ear-mold was properly fitted, the headpiece was quite stable. All of the subjects could wear their headpiece during sports and other physical activities. A properly sized ear-mold was very important to ensure a comfortable, stable fit that exerted no pressure against the concha. The ear-mold fitting technique is similar to that used by many hearing aid dealers. If the magnetless headpiece becomes widely used, the patient ear-mold could be fitted by a hearing aid dealer and simply snapped into the pre-made magnetless headpiece. Most important, the headpiece adhered against the skin firmly enough for reliable signal transmission. There was not a large difference in the voltage power needed between the headpiece and the ICS, or in battery life, between the magnetless implant and the standard Clarion implant.

All patients were very happy with the aesthetics of the headpiece, and felt that the microphone position near the concha was an improvement over the standard magnet-containing design. Further development of the magnetless headpiece also may allow direct connection to other external devices (ie, frequency modulation systems). The headpiece also could be used by patients with a magnetic Clarion cochlear implant who want the benefit of the better microphone position and improved appearance.

With the increasing use of MRI, there will be a greater demand for a magnetless cochlear implant. The results of the MRI compatibility tests were promising. With 1.5- or 0.3-T MRI, there were no significant torque, force, temperature increase, implant damage, or unintentional output. Distortion with 1.5-T MRI consisted of very minor shading with a fast spin echo, improving with a single-shot fast spin echo. There was slightly more distortion with the 0.3-T MRI.

An MRI-compatible implant also would open doors to functional MRI brain research. Functional MRI is a relatively new technique for noninvasive mapping of brain functions. The method detects focal increases in MRI signal that accompany increases in blood flow and tissue oxygen delivery. Functional MRI is preferable to other brain mapping techniques in that it is noninvasive and relatively risk-free, and provides detailed activation maps of the entire brain.[10] With a magnetless cochlear implant patient, we may have the opportunity to stimulate the auditory nerve (via sound, with the speech processor) and to investigate corresponding brain activity. This procedure would allow comparisons with brain function in hearing people, and would help in tailoring optimal speech processing strategies for cochlear implant patients.

REFERENCES

1. Applebaum EL, Valvassori GE. Further studies on the effects of magnetic resonance imaging fields on middle ear implants Ann Otol Rhinol Laryngol 1990;99:801-4.
2. Portnoy WM, Mattucci K. Cochlear implants as a contraindication to magnetic resonance imaging. Ann Otol Rhinol Laryngol 1991;100:195-7.
3. Heller JW, Brackmann DE, Tucci DL, Nyenhuis JA, Chou CK. Evaluation of MRI compatibility of the modified Nucleus multichannel auditory brainstem and cochlear implants. Am J Otol 1996;17:724-9.
4. Weber BP, Neuburger J, Battmer RD, Lenarz T. Magnetless cochlear implant: relevance of adult experience for children. Am J Otol 1997;18:S50-S51.
5. Baumgartner W, Youssefzadeh S, Franz P, Gstoettner W. Magnetic resonance imaging in cochlear implanted patients. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.
6. Chouarde CH, Ouayoun M. Magnetic resonance imaging and cochlear implants. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.
7. Teisse CH, Hochmair ES, Hochmair-Desoyer IJ. Magnetic resonance imaging compatibility of a cochlear implant. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.
8. Weber BP, Goldring JE, Santogrossi T, et al. MRI compatibility testing of the CLARION 1.2 cochlear implant. Am J Otol (in press).
9. Chou CK, McDougall JA, Chan KW. Absence of radiofrequency heating from auditory implants during magnetic resonance imaging. Bioelectromagnetics 1995;16:307-16.
10. Millen SJ, Haughton VM, Yetkin Z. Functional magnetic resonance imaging of the central auditory pathway following speech and pure-tone stimuli. Laryngoscope 1995;105:1305-10.

Ann Otol Rhinol Laryngol 108:1999

SURGICAL TECHNIQUE FOR THE CLARION® COCHLEAR IMPLANT

THOMAS J. BALKANY, MD
MIAMI, FLORIDA

NOEL L. COHEN, MD
NEW YORK, NEW YORK

BRUCE J. GANTZ, MD
IOWA CITY, IOWA

This paper describes a technique for implantation of the CLARION® Multi-Strategy™ Cochlear Implant based upon the authors' surgical experience with the device. Although much of the procedure is similar to many commonly performed otologic operations, including implantation of other cochlear prostheses, several device-specific modifications are highlighted. Those modifications include a substantial bony seat, facial recess, and cochleostomy, and the use of an electrode insertion tool.

KEY WORDS — cochlear implant, surgical technique.

INTRODUCTION

The surgery for cochlear implantation is in many ways similar to other, more commonly performed otologic procedures. However, certain aspects of this operation are unique and deserve special attention. Surgeons proficient in most ear procedures may not be experienced with recessed seating of the implantable electronics package, bone-anchored tie-down sutures, cochleostomy, and electrode insertion, which are singular features of the cochlear implantation operation. In addition, the physical characteristics of the implantable electronics package and the electrode array vary among cochlear implants (CIs), thereby requiring device-specific surgical techniques to minimize complications. Consequently, surgeons familiar with a technique for one device will find certain aspects of that method inappropriate for another device.

Experience with CI surgery has led to the evolution and development of surgical techniques that can simplify the procedure and avoid complications. The purpose of this report is to describe a technique used by the authors specifically for the CLARION® Multi-Strategy Cochlear Implant™ (Advanced Bionics Corporation, Sylmar, Calif). Many other aspects of this procedure are used routinely with all implant devices.

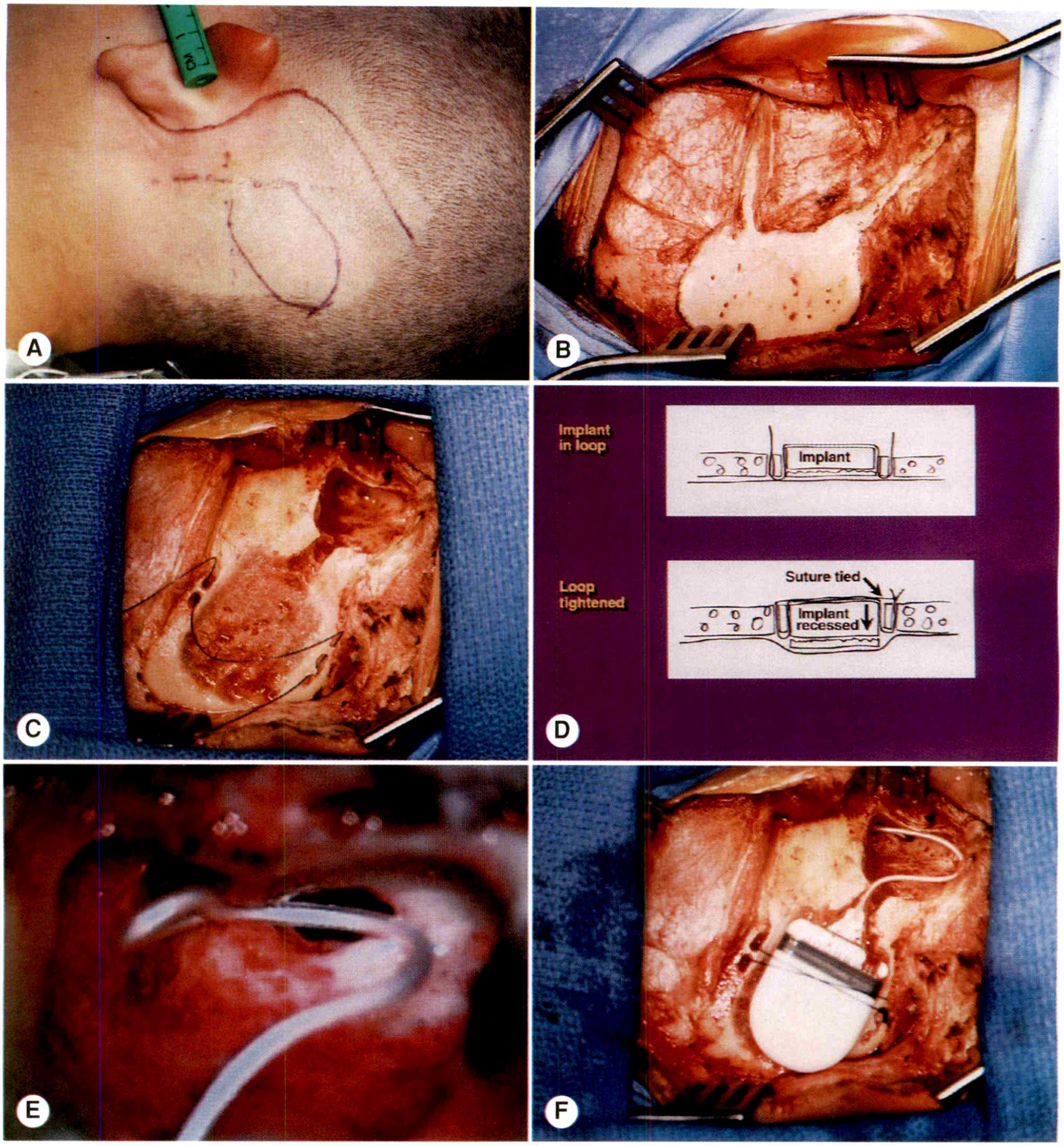
SURGICAL PROCEDURE

Preparation and Draping. Inexperienced CI surgeons often comment that correct location of the incision and device placement are among their greatest concerns. The following guidelines provide a standard procedure that can be modified as the surgeon becomes more experienced. An area 2 finger-widths behind the pinna and extending 3 finger-widths above the pinna is shaved. With the patient in surgical position, a vertical line is lightly drawn at the posterior edge of the flattened pinna. (Because the pinna is smaller in young children, the line must be drawn 5 to 8 mm further posterior in those patients in order to accommodate the ear-level speech processor.) A second horizontal intersecting line is lightly drawn indicating the linea temporalis, overlying the thickest bone in this area. The implantable cochlear stimulator (ICS) template then is placed on the flattest area of the skull in the quadrant formed by these lines with its anterior margin at their intersection, and circumscribed with a marking pen. Thus, the orientation of the template may vary from near-horizontal to near-vertical. In general, the younger the child, the higher or more vertical the device placement (see Figure, A[1]). A facial nerve monitor is used in all cases, and patients routinely receive a single intravenous injection of cephalothin sodium just prior to incision.

Incision. The authors routinely use an extended postauricular incision such as seen in the Figure, A, on a 24-month-old child. A standard mastoidectomy incision is marked just posterior to the postauricular crease and extended 4 to 6 cm in a posterior-superior direction. Its direction is parallel to and 2 cm from the upper margin of the device. In children with exceptionally thin skin, such as those under 18 months of age, the postauricular part of the incision may be placed anterior to the crease, overlying the concha. This modification avoids placing the incision directly over the lead cable if the skin is too thin to create a secondary pericranial flap (see below).

From the Department of Otolaryngology–Head and Neck Surgery, University of Miami Ear Institute, Miami, Florida (Balkany), the Department of Otolaryngology–Head and Neck Surgery, New York University School of Medicine, New York, New York (Cohen), and the Department of Otolaryngology–Head and Neck Surgery, University of Iowa School of Medicine, Iowa City, Iowa (Gantz).

CORRESPONDENCE — Thomas J. Balkany, MD, Dept of Otolaryngology, University of Miami, Box 016960 (D-48), Miami, FL 33101.



Surgical technique for Clarion cochlear implant. A) Device location. Vertical line is drawn at posterior edge of pinna, and horizontal line over linea temporalis. Intersection of vertical and horizontal lines marks anteriormost point of implantable cochlear stimulator (ICS). Device is placed over flattest area within quadrant. Postauricular incision is extended parallel with upper edge of ICS. Methylene blue (1 drop or less) is deposited transcutaneously to mark anteriormost extent of ICS on skull. B) Pericranium. "H"-shaped pericranial incision creates anterior flap, which will cover anterior one third of ICS, and posterior portion that is removed to allow drilling of seat and tie-down holes. C) Bony seat and tie-down suture holes. D) Retraction sutures. This bone-anchored suture, described by Cohen and Kuzma,[1] is used only with dural island and will lower ICS profile to be flush with surrounding bone. E) Facial recess and split bridge. Incus bridge is divided at level between horizontal canal and short process of incus with 1-mm diamond bur. Cable then is press-fit into split, stabilizing electrode array. (In this case, small cavity resulted in redundant cable, and gentle loop was made with second segment of cable fixed in notch.) F) ICS in position. ICS is sutured in bony seat.

Next, the skin is swabbed with povidone iodine and injected with lidocaine hydrochloride–epinephrine at the intersection of the 2 lines (or the apex of the ICS template) and along the incision line. Methylene blue 0.1 mL is deposited through a 25-g needle, and the cranium is lightly abraded to mark the anteroinferior limit of the bony seat. (Only *one* drop of dye should be injected.) The incision is made with a cutting cautery or a cold knife down to the level of the temporalis fascia.

Skin Flap. Beginning superiorly, the flap is elevated in the avascular layer of loose areolar tissue. Access to the most posterior extent of the bony seat is necessary, so the template is again circumscribed, this time over the pericranium, to determine the extent to which the flap must be undermined. The skin flap is held with elastic hooks or self-retaining retractors. The anteriorly based pericranium-fascia incision is shown in the Figure, B. Note that the pericranial flap will overlie the anterior third of the device seat. The flap is elevated and retained in the retractors. In all but very young children, the flap will provide an additional tissue layer where the lead cable crosses the incision. In young children with very thin skin, the same effect is accomplished by placing the incision over the concha and/or elevating the pericranium with the flap. The remainder of the circumscribed pericranium is removed to allow for drilling of the seat and holes for bone sutures. The excised tissue is used later to pack the cochleostomy.

Bone Seat and Bone-Anchored Sutures. In older patients, the template is circumscribed a third time over bone and a custom-fitted bone seat or well is created at least 3 mm deep (see Figure, C). Because the temporal bone is thinner in young children, the bone is thinned until dura can be seen and an island is created that can be depressed, allowing the device to be recessed at least 3 mm. The seat should accommodate the fantail without compressing it.

A 2-mm diamond bur is used to drill connecting tie-down holes above and below the device approximately 2 to 4 mm apart (see Figure, C). If the dural island technique is used, a Freer elevator is used to elevate the dura from beneath the bone and to protect the dura during drilling of retraction tie-down sutures as described by Cohen and Kuzma[1] (see Figure, D).

Mastoidectomy. A complete mastoidectomy is performed leaving overhangs posteriorly, superiorly, and inferiorly. The anterior wall is thinned to allow better visualization of the round window via the facial recess. The horizontal semicircular canal and incus are visualized. The facial nerve is identified positively through an intact mantle of bone, and the facial recess is opened. To ensure sufficient working room, one must be able to pass a 5F suction easily through the facial recess both anteriorly and inferiorly. Care must be taken to avoid damaging the annulus of the tympanic membrane or the canal wall skin. In some cases it will be necessary to sacrifice the chorda tympani by extending the facial recess. The incus bridge is thinned to 2 mm, and a 1-mm diamond bur is used to split the bridge from superior to inferior at a level between the horizontal canal and the short process of the incus[2] (see Figure, E). This split bridge will be used to stabilize the electrode cable. A trough is drilled anterior to the seat to connect with the mastoid cavity.

Cochleostomy. While drilling through the facial recess, care is taken to irrigate continuously the bone covering the facial nerve and to avoid touching this area with the shaft of the bur. The round window membrane must be well identified, because it is the critical landmark for the endosteum of the scala tympani. Drilling is begun anterior and inferior to the membrane until the endosteum is identified. The endosteum then is followed at least 3 mm forward and inferiorly with a 1.5-mm diamond bur, removing the labyrinthine bone of the inferior surface of the basal turn of the cochlea. The area is carefully irrigated, hemostasis is updated, and the endosteum is entered. Edge irregularities are removed with a Hough hoe, thereby creating a large cochleostomy. The surgeon should be able to visualize the scala up to the beginning of the ascending turn in order to avoid blind electrode insertion. Moistened Gelfoam is placed over the cochleostomy until the electrode is inserted. Monopolar cautery units are turned off and unplugged.

Device Insertion. The integrity of the Clarion implant components are tested by telemetry before opening the sterile package. After lifting a corner of the package, the device is flooded with saline to prevent static charge buildup. Then the package is opened fully. Because the Clarion is ear-specific (left versus right) owing to the direction of the spiral curve of the electrode, the ICS is checked to confirm that it is the proper device for the ear to be implanted. The ICS then is secured in the bony seat with permanent sutures, such as 2-0 Ticron™, Tevdek™, or Prolene™ (see Figure, F). The ICS should be almost flush with the edges of the surrounding bone. The knot should be located off the surface of the ICS.

The electrode array comes in a plastic insertion tube that is placed securely on the end of the accompanying insertion tool. Care must be taken to ensure that the insertion tube is fully loaded on the tool. The insertion tube is rotated so that its slot and the shoulder of the electrode face superiorly toward the anterior oval window niche when the tool is held comfortably in the surgeon's hand. Thus, the slot will be rotated to the surgeon's left when operating on a right ear and to the right when operating on a left ear. The tool is held identically in both cases. With the end of the insertion tube fully in the anteriormost extent of the cochleostomy, the electrode is inserted by gently and steadily moving the thumb-slide forward. The surgeon observes the slot for possible buckling of the electrode and feels for resistance to electrode passage. Normally, little or no resistance is felt. The thumb slide is pushed forward all the way, to disengage the electrode from the tube. The tube and tool then are removed. If the electrode does not immediately disengage, it may be released by stabilizing it with an annulus elevator while removing the tool and tube.

An annulus elevator is used to press-fit the electrode lead cable into the split-bridge and under the incus short process, where it is held firmly (see Figure, E). The cable is looped into the mastoid cavity so that it is in contact with the mastoid tegmen for further stabilization. None of the cable should be lateral to the plane of the mastoid cortex. No other tie-down sutures are used.

The excised pericranial tissue is cut into 4-mm squares or strips, and the cochleostomy is packed. Care should be taken not to damage the electrode array. The operative site is irrigated copiously with bacitracin zinc and saline solution. Further hemostasis may be obtained with bipolar cautery, but not within 1 cm of the ICS or cable. The impedances of the electrodes are measured by telemetry using a sterile headpiece and cord. The pericranial flap is closed over the anterior device and the cable in its trough, followed by closure of the incision in layers. A mastoid dressing is applied and the patient is awakened. An intraoperative radiograph is recommended by one of us (N.L.C.).

DISCUSSION

While much of this procedure is common to other CI surgeries, several characteristics of the Clarion procedure are worth highlighting. First, the skin flap must provide access to the entire bony seat. For ceramic implants like the Clarion, the size of the seat encompasses the entire implant, including the anterior fantail at which the electrode wires exit the case. Second, the bony seat should be at least 3 mm deep. Shallow bony excavation, which may be used at times with a flexible package like the Nucleus implant, is inappropriate for the Clarion device. When indicated, drilling the bony island must be done with care, as the transverse sinus usually underlies the island. Furthermore, bone-anchored sutures are required to prevent movement of the ICS.

Third, although the insertion tool greatly facilitates electrode insertion, it requires a larger facial recess and cochleostomy than other devices. It is important to have sufficient working room in order to place the insertion tube in proper position. If the tip is placed partially into the cochleostomy, or at an inappropriate angle, the electrode may begin to assume its curved shape while still in the inferior segment, doubling over on itself. It also is important that the electrode be extruded from the insertion tube in a smooth and continuous motion. After the electrode is inserted, the surgeon should inspect the scala under high-power magnification to verify that the electrode rounds the ascending turn. This verification may eliminate the need for imaging in routine cases, familiarizes the surgeon with the cochlea, and is not possible with blind insertion techniques.

In conclusion, the techniques described here have evolved after experience with several hundred cases and are useful in obtaining safe insertions and avoiding complications. The manufacturer's official guidelines should be followed as well.[3] Nonetheless, the authors recognize that other techniques may be equally effective.

REFERENCES

1. Cohen NL, Kuzma J. Titanium clip for cochlear implant electrode fixation. Ann Otol Rhinol Laryngol [Suppl] 1995;104 (suppl 166):402-3.

2. Balkany TJ, Telischi F. Fixation of the electrode cable during cochlear implantation: the split bridge technique. Laryngoscope 1995;105:217-8.

3. Surgeon's Manual. Advanced Bionics Corporation, Sylmar, California, 1996.

Ann Otol Rhinol Laryngol 108:1999

USING THE CLARION® COCHLEAR IMPLANT IN COCHLEAR OSSIFICATION

PHILIP A. BIRD, MD   THOMAS J. BALKANY, MD   ANNELLE V. HODGES, PHD
STACY BUTTS, MA   ORLANDO GOMEZ, PHD   DAVID LEE, PHD
MIAMI, FLORIDA

This paper is a retrospective review of 5 patients with various degrees of cochlear ossification who were implanted with the CLARION® Multi-Strategy™ Cochlear Implant. Preoperative computed tomography scans, intraoperative findings, surgical technique, and hearing outcomes are discussed in a case report format. Full implantation was achieved in all cases by a systematic approach that included drill-through of proximal obstruction (2 cases), scala vestibuli insertion (2 cases), and complete drill-out (1 case). The only complication was delayed wound healing in a patient with sickle cell disease, chronic active hepatitis, and steroid dependency on antimetabolite therapy. Early results show that the 4 patients with at least 3 months of experience have a mean open-set sentence recognition score of 55% and a mean open-set word recognition score of 24%. The conclusion is that implantation of the Clarion device in ossified cochleas can be successful in all degrees of ossification and can provide significant hearing benefit.

KEY WORDS — cochlear implant, deafness, hearing loss, ossified cochlea.

INTRODUCTION

Ossification of cochlear scalae was once considered a contraindication to cochlear implantation. Over the past decade, however, techniques have been developed to enable successful implantation of all cochleas, regardless of the degree of ossification. Balkany et al[1] described excellent results in partially ossified cochleas. For the completely ossified cochlea, Gantz et al[2] described the total drill-out procedure. Cohen and Waltzman[3] described the short inferior tunnel insertion, and Steenerson et al[4] described scala vestibuli insertion. On the basis of all of these techniques, Balkany et al[5] subsequently suggested a systematic approach to surgery of the ossified cochlea.

To date, most reports of implantation of the ossified cochlea have been with the Nucleus cochlear implant (Cochlear Corporation, Englewood, Colo). The purpose of this report is to describe our experience with the CLARION® Multi-Strategy™ Cochlear Implant (Advanced Bionics Corporation, Sylmar, Calif) in the presence of cochlear ossification.

METHODS

Subjects. Five patients with cochlear ossification who were implanted with Clarion devices were identified from the cochlear implant database at the University of Miami Ear Institute. Details of their clinical presentation, operative findings, radiologic studies, and audiologic testing were reviewed.

Speech Testing. All postoperative speech testing was performed in an American National Standards Institute–approved calibrated sound suite with compact disk or audiotape recordings of test materials. Speech reception threshold (SRT) or speech awareness threshold (SAT) was evaluated with recorded spondee words.

Speech recognition was assessed with Central Institute for the Deaf Everyday Sentences Test (CID sentences) and Northwestern University Phonetically Balanced Monosyllable Word Test (NU6 word) lists. Test materials were presented at 70 dB sound pressure level (SPL) in a sound field, with the patient setting the device to the preferred listening level. Face-to-face communication benefit from the implant was assessed with the Visual Enhancement subtest of the Minimal Auditory Capabilities Battery. These measures were presented in a quiet room with the tester seated approximately 1 m in front of the patient. Materials were presented at normal conversational speech levels in both implant-off and implant-on conditions. For all speech tests, the most recent scores are reported here.

Surgical Technique. Surgical technique followed the manufacturer's recommendations through the cochleostomy step.[6] To summarize, the implantable cochlear stimulator (ICS) was placed in a deep bony seat and fixed with bone-anchored, nonabsorbable suture, the facial recess was widely opened, the cochleostomy was elongated to 3 mm to facilitate controlled insertion of the electrode, and the cable was fixed in a 1-mm-slot "split bridge" drilled in the incus buttress to prevent electrode extrusion.[7]

From the Departments of Otolaryngology (Bird, Balkany, Hodges, Butts) and Epidemiology and Public Health (Gomez, Lee), University of Miami Ear Institute, Miami, Florida.

CORRESPONDENCE — Thomas J. Balkany, MD, University of Miami Ear Institute, PO Box 016960 (D-48), Miami, FL 33101.

RESULTS

Patient	Age at Surgery (y)	Extent of Cochlear Drilling	CI Use Prior to Testing	SRT/SAT (dB)	CID (%)	NU6 (%)	Visual Enhancement* Without CI (%)	Visual Enhancement* With CI (%)
1	70	Drill-through	3 y 10 mo	40	32	10	77	97
2	18	Drill-through	3 mo	25	42	24	DNT	DNT
3	24	Scala vestibuli	4 mo	30†	99†	36†	36†	98†
4	80	Scala vestibuli	7 mo	25	47	24	43	91
5	6	Total drill-out	None	NA	NA	NA	NA	NA
Mean				30	55	24	52	93

CI — cochlear implant, SRT — speech reception threshold, SAT — speech awareness threshold, CID — Central Institute for the Deaf Everyday Sentences, NU6 — Northwestern University Monosyllable Word Test, DNT — did not test, NA — not available.

*Visual enhancement testing compares communication using visual input only with communication using both visual and auditory input.

†Spanish materials.

Because of cochlear ossification, we followed the systematic approach to electrode insertion described by Balkany et al.[5] An inferior-segment tunnel was created anterior to the cochleostomy, following the abnormal bone. Often, the unobstructed distal lumen of the scala tympani will be reached after a few millimeters of drilling (the "drill-through" technique, used on 2 patients in the series). If the lumen was not located or if slight bleeding was encountered (suggesting that the vasa vasorum of the internal carotid artery may have been reached), drilling was stopped at a distance of 8 mm from the round window membrane. At this point, the scala vestibuli was opened and, if patent, the electrode array was inserted. If both scalae were obstructed, a cochlear drill-out procedure was performed, with the original tunnel preserved for fixation and an intact-canal-wall technique used without obliteration.[8]

CASE REPORTS

Case 1. A 69-year-old woman presented with profound hearing loss secondary to otosclerosis. She had undergone a left stapedectomy previously. Preoperative computed tomography (CT) scanning suggested bilateral labyrinthine demineralization and scalar ossification, which was worse on the left side. The patient underwent cochlear implantation in her right ear.

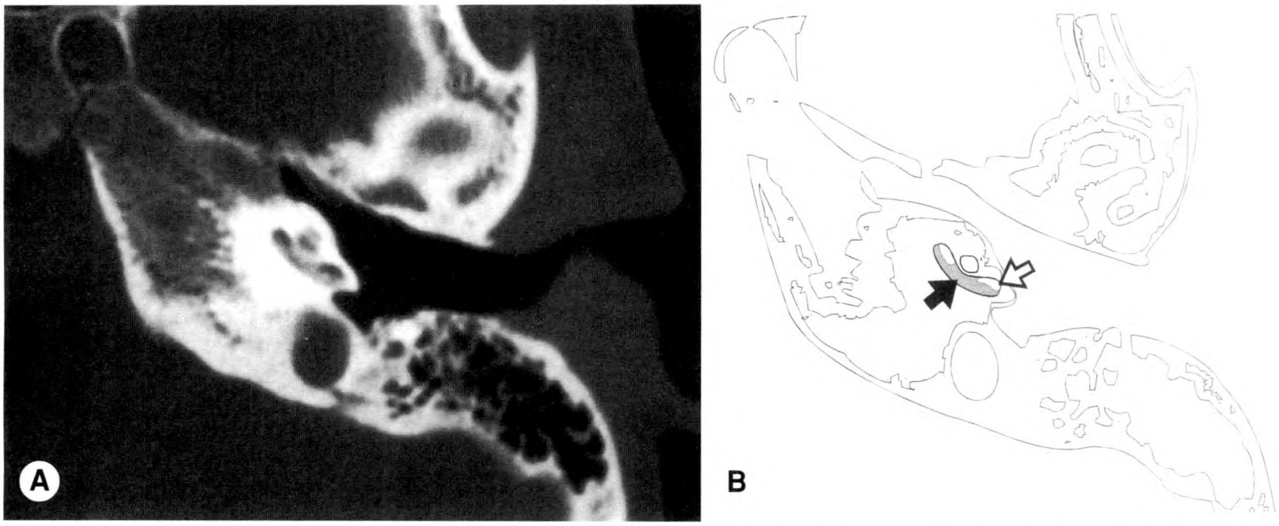
During surgery, the round window niche and membrane were found to be obliterated by otosclerotic bone extending 4 mm along the scala tympani. Distal to the obliteration, the lumen was patent for 3 mm. Another small collection of otospongiotic tissue was encountered approximately 7 mm from the round window. The obstructing bone was cleared with the drill and microinstruments, and a Clarion cochlear implant was inserted. At the initial insertion, resistance was noted and the electrode was withdrawn. A second insertion resulted in easy placement of all electrodes. Perioperative testing revealed satisfactory impedance values for all electrodes. Hearing results are noted in the Table.

Case 2. An 18-year-old St Croix, US Virgin Islands, resident with sickle cell trait developed autoimmune chronic active hepatitis for which she received azathioprine sodium and oral steroid treatment. Eighteen months prior to surgery, she developed sudden, profound hearing loss in the left ear. Three months later, she developed sudden, profound hearing loss in the right ear. Neither episode responded to an increased steroid dose. Preoperative CT scanning revealed an increase in density in the region of both round windows, worse on the left side. A right-ear cochlear implant procedure was performed.

During surgery, the scala tympani was found to be ossified for approximately 8 mm from the round window membrane, but was patent distal to that point. A Clarion 1.2 cochlear implant was fully inserted without difficulty. Perioperative testing revealed satisfactory impedance values for all electrodes.

On the third postoperative day, the patient developed a small hematoma in the inferior portion of the wound, which was managed with in-office drainage and oral antibiotics. By the fifth postoperative day, there was superficial wound dehiscence. Both problems were thought to be related to sickle cell trait, chronic active hepatitis, steroid dependence, and use of the antimetabolite. She was treated with intravenous antibiotics and local wound care. The wound healed without further incident over a 3-week period. Cultures of the wound were negative throughout. Hearing results are shown in the Table.

Case 3. A 24-year-old woman was found to have pneumococcal meningitis after a raft escape from Cuba to the United States. She subsequently developed anacusis in the right ear and profound hearing loss in the left ear. Preoperative CT scanning revealed evidence of cochlear ossification, more extensive on



(Case 3) Ossification of scala tympani (solid arrow) and areas of less density (open arrow) corresponding to patent scala vestibuli. A) Preoperative axial computed tomogram. B) Artist's representation of A.

the right side than on the left. The left cochlea (see Figure) shows a pattern that indicated preoperatively a possible obstruction of the scala tympani with patency of the scala vestibuli.

A left cochlear implant procedure was performed. During surgery, the round window and scala tympani were found to be ossified. The lumen was drilled out for a distance of 8 mm, and ossification was found to be present around the ascending turn. At this point, the scala vestibuli was opened and found to be patent. A Clarion 1.2 device was fully inserted without difficulty. Perioperative testing revealed satisfactory impedance values for all electrodes. There were no postoperative complications. Hearing results are shown in the Table.

Case 4. An 80-year-old man had undergone right cochlear nerve section for tinnitus in 1957. He subsequently underwent at least 2 procedures on his left ear for cholesteatoma, resulting in a canal-wall-down mastoidectomy cavity. Subsequently, he developed profound sensorineural hearing loss on the left side.

The left ear was implanted with a Nucleus device in 1993, combined with radical mastoidectomy and obliteration. Almost $2^1/2$ years later, he developed an intradermal bulla overlying the receiver-stimulator, which was incised by another physician. This procedure led to implant exposure and ultimately required removal of the device. The electrode array was separated from the receiver-stimulator and left in the cochlea.

Approximately 10 months later, he was reimplanted with a Clarion device by choice in the same ear. There was bony and fibrous obstruction of the inferior segment of scala tympani. The obstruction was followed to the ascending turn, where a combination of bony stenosis and fibrous tissue prevented implantation of the Clarion electrode array, which is larger than the Nucleus array. The scala vestibuli then was opened and found to be patent. The Clarion device was fully inserted without difficulty. Perioperative testing revealed satisfactory impedance values for all electrodes. There were no postoperative problems.

Case 5. A 6-year-old Brazilian boy was deafened by *Haemophilus influenzae* meningitis at 20 months of age. Preoperative CT scanning revealed changes consistent with extensive ossification bilaterally, worse on the left side than the right. A right cochlear implant procedure was performed.

During surgery, the scala tympani was found to be ossified to 8 to 9 mm. The scala vestibuli also was ossified. A cochlear drill-out procedure then was performed with preservation of the bony external auditory canal and tunnel. At the end of the ossified basal turn, the lumen of the cochlea was patent. The electrode was placed into the circum-modiolar trough with its tip extending into the lumen of the second turn. Perioperative testing revealed satisfactory impedance values for all electrodes. There were no postoperative complications.

Hearing Results. Hearing results for the 4 subjects with at least 3 months of implant experience are shown in the Table. All subjects achieved open-set speech recognition and visual enhancement with their implants. The SRT and SAT ranged from 25 to 40 dB hearing level (HL), with a mean of 30 dB HL. The CID sentence scores ranged from 32% to 99%, with a mean of 55%. The NU6 word scores ranged from 10% to 36%, with a mean of 24%. The case 5 patient has not had his device programmed as of this writing.

DISCUSSION

This series of patients demonstrates the technical feasibility and efficacy of using the Clarion cochlear implant in an ossified cochlea. Cochleas with all degrees of ossification were implanted without difficulty. Several points can be made on the basis of our experience with these patients.

First, preoperative CT scanning proved very accurate in predicting significant ossification. The procedure identified ossification in cases 1, 2, 3, and 5 of this series. (Patient 4 was not imaged preoperatively, since his Nucleus electrode had been left in position, accurate surgical records were available, and his right ear could not be implanted because of previous right cochlear nerve section.) Of particular interest here is the preoperative CT finding in case 3 (see Figure). A preoperative prediction of ossification involving the scala tympani but not the scala vestibuli was made and confirmed during surgery.

Our previous experience with preoperative CT scanning in surgically proven cases of ossification is that ossification was correctly identified in 20 of our total series of 30 patients (67%).[8] In those cases not identified, ossification involved 4 mm or less of the inferior segment of the basal turn. Our data are in agreement with other reports regarding the utility of preoperative CT scanning.[9,10]

Second, inserting the Clarion electrode array into the scala vestibuli instead of the scala tympani was successful. Scala vestibuli insertion with the Nucleus device was first described by Steenerson et al.[4] Theoretically, the larger electrode of the Clarion device could prove difficult to insert into the scala vestibuli. However, this difficulty did not occur here in case 3. A possible explanation is that the electrode may have occupied both the scala vestibuli and scala media, whose combined diameters approximate that of the scala tympani (R. Schindler, personal communication, 1997). An alternate explanation may be that ossification did not conform to the scalar anatomy.

Third, when performing a scala tympani or vestibuli insertion after an incomplete cochlear drill-out, the starting point of insertion may be up to 7 to 8 mm from the round window membrane. In that situation, the electrode array will have reached the desired depth of insertion (25 mm from the round window) before it has completely left the insertion tool. In those cases, as resistance is encountered, the surgeon should slowly withdraw the insertion tool while the electrode is disengaging.

Notably, a somewhat complicated postoperative course occurred in case 2. Because the patient had sickle cell trait chronic active hepatitis and was immunocompromised by steroid dependency and antimetabolites, the wound problem was not surprising. Fortunately, only the most superficial layer of the wound was involved, so that device exposure did not occur and the skin eventually healed within 10 days. Her early device performance is very encouraging.

Finally, the hearing results for patients with ossified cochleas are good. Although only short-term follow-up is available on cases 1 to 4, we would expect further improvement to occur with more experience. The performance in these cases is comparable to that of our larger series of ossified cochlear implants (unpublished data) and those of others.[1] In general, patients with incomplete ossification can expect results similar to those achieved in patients who have nonossified cochleas. However, patients with total drill-outs may have poorer but acceptable results.

CONCLUSION

The Clarion cochlear implant is relatively safe and effective for patients with all degrees of cochlear ossification.

REFERENCES

1. Balkany T, Gantz B, Nadol JB Jr. Multichannel cochlear implants in partially ossified cochleas. Ann Otol Rhinol Laryngol [Suppl] 1988;97(suppl 135):3-7.

2. Gantz BJ, McCabe BF, Tyler RS. Use of multi-channel cochlear implants in obstructed and obliterated cochleas. Otolaryngol Head Neck Surg 1988;98:72-81.

3. Cohen NC, Waltzman SB. Partial insertion of the Nucleus multi-channel cochlear implant: technique and results. Am J Otol 1993;14:357-61.

4. Steenerson RL, Gray LB, Wynens MS. Scala vestibuli cochlear implantation for labyrinthine ossification. Am J Otol 1990;11:360-3.

5. Balkany T, Gantz BJ, Steenerson RL, Cohen NL. A systematic approach to electrode insertion in the ossified cochlea. Otolaryngol Head Neck Surg 1996;114:4-11.

6. Surgeons' Manual: CLARION® Multi-Strategy™ Cochlear Implant, Advanced Bionics Corporation, Sylmar, California, 1996.

7. Balkany T, Telischi FF. Fixation of the electrode cable during cochlear implantation: the split bridge technique. Laryngoscope 1995;105:217-8.

8. Balkany T, Luntz M, Telischi FF, Hodges AV. Intact canal wall drillout of implantation of the totally ossified cochlea. Am J Otol 1997;18:58-9.

9. Jackler RK, Luxford WM, Schindler RA, McKerrow WS. Cochlear patency problems in cochlear implantation. Laryngoscope 1987;97:801-5.

10. Langman AW, Quigley SM. Accuracy of high-resolution computed tomography in cochlear implantation. Otolaryngol Head Neck Surg 1996;114:38-43.

Ann Otol Rhinol Laryngol 108:1999

IMPLANTATION OF THE CLARION® COCHLEAR IMPLANT IN AN OSSIFIED COCHLEA

LEE A. HARKER, MD
NATALIE GENTILE, MA
DEBORAH VEAZEY, MS
ELIZABETH MCCLEARY, MA
OMAHA, NEBRASKA

This report describes the successful implantation of the CLARION® Multi-Strategy™ Cochlear Implant electrode in the totally ossified cochlea of a 5-year-old child via a radical mastoidectomy approach. Postoperatively, the child demonstrated responses to auditory stimuli, even though the electrode array contacted only bone and muscle graft tissue with no visible evidence of nerve fibers or cochlear lumen. Responses to sound did not begin to emerge until 10 weeks following initial stimulation and improved slowly over time. Although the child's postoperative auditory performance is more limited than that of most implanted children, she derives substantially more benefit from her implant than she did from conventional hearing aids.

KEY WORDS — cochlear implant, ossified cochlea.

INTRODUCTION

Cochlear ossification frequently occurs following deafness from meningitis.[1] In such cases, the obstructive intracochlear bone and soft tissue often requires modifications in surgical technique for insertion of a multichannel cochlear implant electrode array.[2-4] Gantz et al[3] described a technique that allowed for placement of the complete electrode of the Nucleus 22-channel cochlear implant array into a groove corresponding to the basal turn of the cochlea created during a radical mastoidectomy surgical approach. Following the use of this surgical technique in a postlingually deafened adult, Gantz et al reported implant benefit similar to that reported for patients with normal cochlear anatomy.

In children, however, several reports suggest that postoperative benefit following implantation in a completely ossified cochlea may not be evident after 5 or more months of device use.[5,6] In these studies, the children failed to demonstrate improved sound detection, either to electrical stimulation during device fitting or to acoustic stimuli during everyday use, until they had used their implants for a substantial period of time. This phenomenon has been termed "delayed perception." The underlying cause of delayed perception is unknown. Suggested hypotheses include cochlear inflammation secondary to trauma from the drill-out procedure and/or changes in the conducting properties of the surrounding bone or underlying neural elements following the introduction of electrical current.

Published results with the Gantz technique have been limited to the use of the Nucleus implant system with a straight-thin electrode. The precoiled, modiolar-hugging electrode properties of the CLARION® Multi-Strategy™ Channel Cochlear Implant, together with its insertion tool system, might present difficulties for such a procedure. This report describes the successful implantation of the Clarion electrode in the totally ossified cochlea of a 5-year-old child via the surgical technique described by Gantz et al.[3] In addition, 12-month post-stimulation follow-up results are presented.

CASE REPORT

The patient developed total loss of hearing at age 17 months following bacterial meningitis and was first seen at Boys Town National Research Hospital for consideration of a cochlear implant at age 5 years. At that time, she was enrolled in a self-contained preschool setting utilizing total communication and was living at home with her parents and 4-year-old sister. Preoperative audiometric results obtained under earphones revealed responses only at 250 and 500 Hz at 100 and 115 dB hearing level (HL), respectively, in each ear. Aided sound field results with appropriate acoustic amplification revealed a response at 250 Hz at 70 dB HL, with no measurable responses at any other frequency. The preoperative audiologic data suggest that the patient responded to acoustic stimuli on the basis of vibrotactile rather than auditory sensation.[7] She wore bilateral hearing aids even though she received minimal benefit from them. Computed tomographic scans revealed near-total ossification of both cochleas (Fig 1).

From Boys Town National Research Hospital, Omaha, Nebraska.

CORRESPONDENCE — Lee A. Harker, MD, Boys Town National Research Hospital, 555 N 30th St, Omaha, NE 68131.

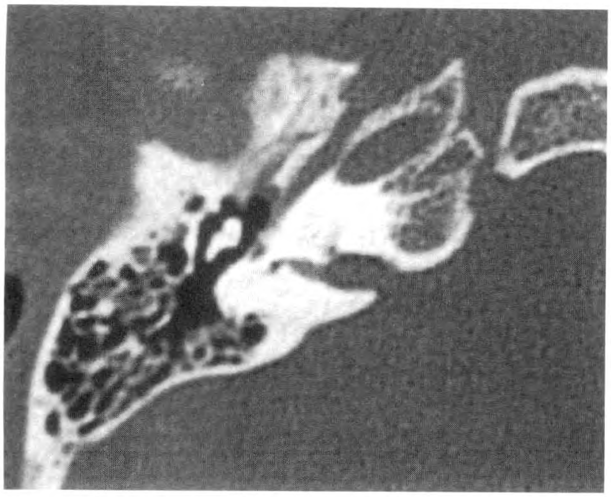


Fig 1. Computed tomography scan showing total ossification of one cochlea.

SURGICAL PROCEDURE

After evaluation and an explanation of the uncertainties and potential risks as well as the potential benefits of the proposed surgery, the patient underwent a radical mastoidectomy approach for a basal cochlear turn "drill-out" procedure to place a Clarion implant into a surgically created trough in her right ear. A groove approximately 2 mm in depth was created from the round window niche anteriorly to the region in which the basal cochlear turn begins its spiral, preserving a complete lip of inferior cochlear wall near the round window to provide postoperative electrode stability. At the anterior cochlear limits, a faint gray shadow was evident, providing guidance for following the curve of the basal turn. Otherwise, there was no evidence of any cochlear lumen — only dense bone indistinguishable by color or characteristics from the adjacent bone. Partial removal of anterior osseous external auditory canal bone improved exposure for further anterior-superior cochlear dissection, and a bony trough $1^1/_2$ to 2 mm deep was created. After the implantable cochlear stimulator (ICS) was fixed into its bed, the electrode was molded manually, laid into the trough, and secured with a temporalis muscle pack bolstered by an adipose tissue obliteration of the middle ear and mastoid cavity. Six electrode pairs lay within the surgically created groove. The medial external auditory canal and tympanic membrane were amputated, and the remaining canal skin was everted and sutured closed. There were no postoperative complications. Postoperative radiographs confirmed the electrode position in the groove corresponding to the cochlea (Fig 2).

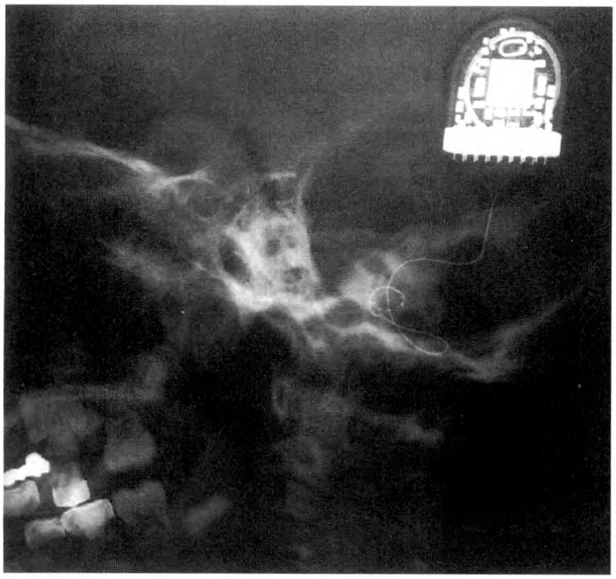


Fig 2. Postoperative radiograph showing electrode positioned in groove corresponding to right cochlea.

TABLE 1. ELECTRICAL THRESHOLD LEVELS IN CLINICAL UNITS ESTABLISHED ON MEDIAL ELECTRODES WITH PULSATILE STIMULATION OVER TIME

	Months Following Initial Stimulation			
Electrode	*3*	*4*	*6*	*12*
1	726	594	486	257
2	726	556	503	266
3	NR	751	657	294
4	NR	NR	887	360
5	NR	NR	887	398
6	NR	NR	887	520

Data are Clinical Units.
NR — no response at system limits.

POSTOPERATIVE RESULTS

The patient was fitted with the Continuous Interleaved Sampler strategy with monopolar stimulation. No consistent responses to electrical stimulation were noted during the initial stimulation session or 2 weeks later, even when the pulse width was widened to 300 microseconds. The first responses to electrical stimulation were noted 10 weeks following the initial stimulation, but they were inconsistent. More consistent responses were observed over time. Table 1 summarizes the electrical threshold data (in Clinical Units) at the 3-, 4-, 6-, and 12-month programming sessions. Threshold levels decreased over time, with the lowest levels obtained at the 12-month visit. Even these levels, however, are substantially higher than those demonstrated by most other Clarion users at our center, who typically are stimulated with a much narrower pulse width (ie, 75 microseconds). Also, at the 12-month visit, the patient reported loudness growth with increasing current levels only on electrodes 1 to 3.

Table 2 shows the sound-field responses obtained while the patient was wearing her Clarion speech

TABLE 2. WARBLE TONE AND SPEECH AWARENESS THRESHOLDS OBTAINED IN SOUND FIELD WITH CLARION COCHLEAR IMPLANT

Frequency (Hz)	*Months Following Initial Stimulation* 3	4	6	12
250	65	70	75	45
500	85	55	90	50
1,000	NR	NR	NR	55
2,000	NR	NR	NR	50
4,000	NR	NR	NR	80
SAT	60	55	100	45

Data are decibels hearing level.

NR — no response at limits of audiometer, SAT — speech awareness threshold.

processor. Again, the lowest responses to acoustic stimuli were obtained at the 12-month visit. These thresholds also are higher (poorer) than those typically seen in other Clarion users.

A battery of closed- and open-set speech perception measures was administered to the patient preoperatively and postoperatively after 3, 6, and 12 months of implant use. She demonstrated performance at chance levels on all of these measures, even at the 12-month postoperative visit. There was no formal assessment of lipreading enhancement with the implant. Observation of her everyday performance, however, indicated improved lipreading performance with the implant.

The Meaningful Auditory Integration Scale (MAIS)[8] and the Meaningful Use of Speech Scale (MUSS)[9] also were administered preoperatively and postoperatively. These procedures employ a structured interview technique to obtain information from the parent about the frequency with which the child demonstrates a set of 10 different auditory (MAIS) or speech (MUSS) behaviors in everyday situations. For each of the 10 behaviors, specified in a set of questions or probes, a rating is assigned based on the frequency of occurrence of the target behavior (0 = never; 1 = rarely; 2 = occasionally; 3 = frequently; 4 = always).

Table 3 shows the total MAIS and MUSS scores (40 points possible) for the patient over time. The results show an improvement of 7 points on the MAIS and 15 points on the MUSS after 12 months of implant use. Improvement on the MAIS reflects increased responsiveness to her name when called in quiet, alerting to environmental sounds in familiar and new environments, and emerging recognition of environmental sounds. In addition, the patient wears her implant all waking hours and is able to detect a device malfunction (eg, dead battery). The 12-month score on the MUSS reflects her increased use of vocalizations with and without signs, and improved vocal quality and control compared to her preimplant performance.

TABLE 3. PREOPERATIVE AND POSTOPERATIVE SCORES ON MAIS AND MUSS

Measure	*Preop*	*3 Months*	*6 Months*	*12 Months*
MAIS	4	9	8	11
MUSS	3	7	10	18

MAIS — Meaningful Auditory Integration Scale, MUSS — Meaningful Use of Speech Scale.

DISCUSSION

The results of this report revealed that the radical mastoidectomy approach for cochlear implantation in totally ossified cochleas can be relatively safely adapted to the Clarion cochlear implant. Auditory responses to electrical stimulation were obtained when the electrode array was placed in a bony groove near the modiolus. Responses were elicited even though there was no visible evidence of nerve fibers or a cochlear lumen, and electrodes contacted only bone and muscle graft tissue. The current levels required to elicit auditory responses, however, were higher than in a structurally normal cochlea, because the electrodes were contacting bone without visible nerve fiber endings. Over time, there was a progressive decrease in electrical auditory thresholds on all electrodes, proceeding from apical to basal electrodes. The improvement in electrical auditory thresholds was accompanied by the appearance and subsequent improvement in warble-tone and speech awareness thresholds. Improvements in warble-tone thresholds appeared first for low-frequency stimuli, and then were detected for progressively higher-frequency stimuli.

Although the patient demonstrated more limited auditory abilities with her implant than most other children, her scores on the MAIS and MUSS, as well as subjective impressions and observations, indicate that she obtained substantially more benefit from her implant than she did from conventional hearing aids. Responses to sound were delayed, consistent with the reports of other children following implantation in a totally ossified cochlea.[5,6] Further improvement in her skills is expected with continued implant use.

REFERENCES

1. Green JD, Marion MS, Hinojosa R. Labyrinthitis ossificans: histopathologic consideration for cochlear implantation. Otolaryngol Head Neck Surg 1991;104:320-6.

2. Balkany T, Gantz B, Nadol JB Jr. Multichannel cochlear implants in partially ossified cochleas. Ann Otol Rhinol Laryngol [Suppl] 1988;97(suppl 135):3-7.

3. Gantz BJ, McCabe BF, Tyler RS. Use of multi-channel cochlear implants in obstructed and obliterated cochleas. Otolaryngol Head Neck Surg 1988;8:72-81.

4. Cohen NC, Waltzman SB. Partial insertion of the Nucleus multi-channel cochlear implant: technique and results. Am J Otol 1993;14:357-61.

5. Geier L, Gilden J, Luetje CM, Maddox HE III. Delayed perception of cochlear implant stimulation in children with postmeningitic ossified cochleae. Am J Otol 1993;14:556-61.

6. Novak MA, Fifer RC, Barkmeier JC, Firszt JB. Labyrinthine ossification after meningitis: its implications for cochlear implantation. Otolaryngol Head Neck Surg 1990;103:351-6.

7. Boothroyd A, Cawkwell S. Vibrotactile thresholds in pure-tone audiometry. Acta Otolaryngol (Stockh) 1970;69:381-7.

8. Robbins AM, Renshaw JJ, Berry SW. Evaluating meaningful auditory integration in profoundly hearing-impaired children. Am J Otol 1991;12(suppl):144-51.

9. Robbins AM, Osberger MJ. The Meaningful Use of Speech Scale (MUSS). Indianapolis, Ind: Indiana University School of Medicine, 1990.

Ann Otol Rhinol Laryngol 108:1999

MULTICHANNEL COCHLEAR IMPLANTATION IN CHILDREN WITH LARGE VESTIBULAR AQUEDUCT SYNDROME

LEE A. HARKER, MD
SCOTT VANDERHEIDEN, MD
DEBORAH VEAZEY, MS
NATALIE GENTILE, MA
ELIZABETH MCCLEARY, MA
OMAHA, NEBRASKA

This study examined the postoperative performance of multichannel cochlear implantation in children with severe-to-profound sensorineural hearing loss secondary to large vestibular aqueduct syndrome. Five children between ages 4 and 13 years who had large vestibular aqueducts confirmed by computed tomography scans underwent implantation of a CLARION® Multi-Strategy™ Cochlear Implant between January 1995 and June 1996 at Boys Town National Research Hospital. In addition to preoperative evaluations, they were examined postoperatively with their implants on a battery of open-set speech recognition tests at 3, 6, 12, and 18 months following initial stimulation. Results indicated a noticeable improvement in open-set speech recognition within the first 3 months of implant use compared to preimplant performance with hearing aids. All 5 patients demonstrated substantial benefit from their implants, but there was variation among the children in the rate and amount of improvement in speech recognition skills.

KEY WORDS — cochlear implant, large vestibular aqueduct syndrome, Mondini malformation.

INTRODUCTION

> The dilated vestibular aqueduct with or without a true Mondini cochlear deformity is associated with progressive deafness and these patients become suitable candidates for an implant, although to my knowledge no implants in such cases have been described.
>
> P. D. Phelps[1(p968)]
> November 1992

In 1791, Carlo Mondini[2] reported an anatomic dissection of the inner ears of an 8-year-old boy who had a congenital malformation that consisted of a dilated vestibule, and a cochlea with a hollow cavity at its apex with fewer than normal turns. Enlargement of the vestibular aqueducts and the endolymphatic sac also was observed. Since that first report, the term Mondini dysplasia has been used by various authors to represent either the typical deformity that Mondini described, or cases with different varieties of developmental aberrations involving any of the vestibular or cochlear turns.

Typical Mondini dysplasia is characterized by an osseous cochlear capsule that is flattened from base to apex with reduction of the normal $2^{1}/_{2}$ turns to 1 to $1^{1}/_{2}$ turns. The modiolus is hypoplastic, often with aplasia of the interscalar septum, resulting in a hollow cavity at the apex. However, the anatomy of the basal cochlear turn is usually mostly preserved. Often, in addition to the enlarged vestibule, there are deformities of 1 or more of the semicircular canals. The vestibular aqueduct also is frequently enlarged, and hydrops of the endolymphatic duct and sac contained in it may occur. Reduction of the number of spiral ganglion cells has been reported as well, to as low as one fourth to one half of the normal 33,000.[3] An aberrant pathway of the facial nerve occasionally occurs concurrent with Mondini dysplasia. The malformation may involve one or both ears.

The large vestibular aqueduct syndrome (LVAS) was named by Valvassori and Clemis[4,5] in 1978, when they described radiographic findings in con-

TABLE 1. PATIENT INFORMATION

Patient	*Sex*	*Ear Implanted*	*Surgery Date*	*Age at Surgery*	*Age Hearing Loss Identified*	*Duration of Profound Deafness (mo)*
1	F	R	June 24, 1996	12 y 11 mo	5 mo	6
2	M	R	Oct 16, 1995	4 y	1 y 11 mo	5
3	M	L	April 15, 1996	10 y 4 mo	4 y 11 mo	3
4	F	R	April 22, 1996	9 y 9 mo	3 y 1 mo	11
5	F	L	Aug 7, 1995	7 y 5 mo	2 y 10 mo	4

From Boys Town National Research Hospital (Harker, Veazey, Gentile, McCleary) and Creighton University School of Medicine (Vanderheiden), Omaha, Nebraska.

CORRESPONDENCE — Lee A. Harker, MD, Boys Town National Research Hospital, 555 N 30th St, Omaha, NE 68131.

TABLE 2. SUMMARY OF RADIOGRAPHIC FINDINGS

Patient	*Cochlea*	*Vestibule*	*Semicircular Canals*	*Vestibular Aqueduct*
1	Normal base; abnormal apex	Normal	Normal	Enlarged
2	Normal base; abnormal apex	Enlarged	Normal	Enlarged
3	Normal	Normal	Normal	Enlarged
4	Normal	Normal	Normal	Enlarged
5	Normal	Normal	Normal	Enlarged

genitally malformed inner ears. They found LVAS to be the most common radiographically detectable inner ear anomaly. Enlarged vestibular aqueducts may occur as an isolated anomaly or in association with other inner ear malformations. Of the 30 cases of large vestibular aqueducts described by Valvassori and Clemis, 13 occurred as an isolated radiographic finding and 17 occurred with other anomalies. Large vestibular aqueducts frequently occur concomitant with cochlear deformities such as aplasia, hypoplasia, and Mondini dysplasia. Typically, the malformation occurs bilaterally.

The enlargement is defined as an anteroposterior diameter of the aqueduct greater than 1.5 mm (normal 0.4 to 1.0 mm) evident on computed tomography, measured midway between the external aperture of the aqueduct and the common crus. It is proposed that an arrest in development during the fifth to seventh week of gestation causes the shorter, larger-caliber aqueduct.[6]

A strong association of sensorineural hearing loss with LVAS has been noted, often with a typical clinical course.[7-10] Commonly, the hearing in a child with LVAS deteriorates in a stepwise fashion in association with an incident of minor head trauma, exercise, or an upper respiratory tract infection. The loss may be negligible or progress to profound levels bilaterally.

The cause of the hearing loss is uncertain. One proposed mechanism for damage involves trauma-induced reflux of hyperosmolar endolymph from the endolymphatic sac through the enlarged duct, damaging the cochlear neuroepithelium. Another theory suggests that the membranous labyrinth of the cochlea is weakened, and trauma causes rupture and mixing of endolymph and perilymph resulting in hearing loss. A third postulate invokes the transmission of abnormal pressure from the posterior fossa through the enlarged vestibular aqueduct and endolymphatic sac and duct during sneezing, coughing, or trauma, rupturing the delicate intracochlear membranes.

Cochlear implantation has proven to be effective in increasing both auditory perception and speech production in children with congenital and acquired deafness from diverse causes. Several studies in patients with either the LVAS or malformed cochleas such as Mondini dysplasia showed favorable responses to implantation of both the single-channel 3M/House cochlear implant and the Nucleus 22 device,[11-16] but to our knowledge, no studies have reported implantation of the CLARION® Multi-Strategy™ Cochlear Implant in LVAS.

METHODS

A retrospective review of children who received multichannel cochlear implants at Boys Town National Research Hospital between October 1991 and June 1996 revealed that 5 patients, ages 4 to 13 years (mean 8.9 years) had LVAS confirmed by computed tomography. All received a Clarion multichannel cochlear implant between August 1995 and June 1996 during the US Food and Drug Administration–moni-

TABLE 3. AUDIOMETRIC RESULTS PRIOR TO TIME OF SIGNIFICANT PROGRESSION OF HEARING LOSS

			Frequency (Hz)				
Patient	*Age*	*Ear*	*250*	*500*	*1,000*	*2,000*	*4,000*
1	9 mo	L	50	60	70	80	90
		R	50	60	70	80	90
2	1 y 11 mo	L	NR	NR	NR	NR	NR
		R	60	70	70	75	95
3	4 y 11 mo	L	DNT	40	20	5	10
		R	NR	NR	NR	NR	NR
4	3 y 1 mo	L	35	45	60	45	55
		R	35	45	60	45	55
5	2 y 10 mo	L	40	35	50	15	15
		R	70	65	60	60	70

Data are decibels hearing level.
NR — no response at limits of audiometer, DNT — did not test.

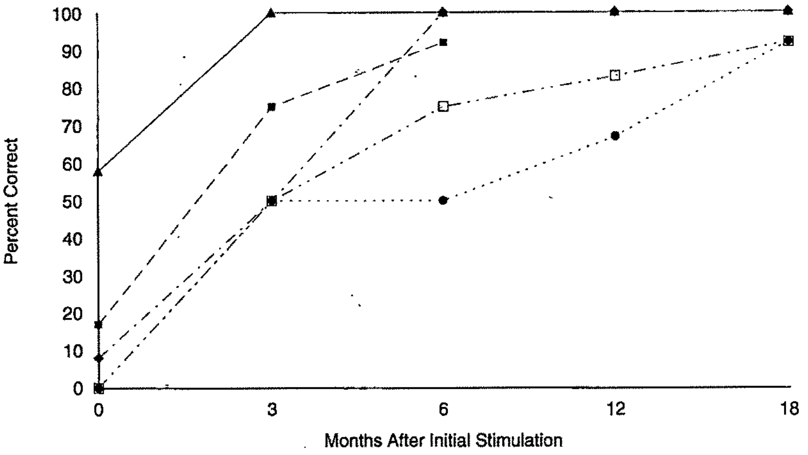


Fig 1. Percent correct scores for Glendonald Auditory Screening Procedure (words) as function of time after implantation. Dark squares — patient 1; light squares — patient 2; diamonds — patient 3; circles — patient 4; triangles — patient 5.

tored clinical trial of the device. Patient information is presented in Table 1.

Radiographic findings are summarized in Table 2. All patients had enlarged vestibular aqueducts and, for 3 of the patients, it was the only abnormality. Two of the children had abnormal cochleas of the type described in Mondini's original case with a normal basal turn and confluence of the apical turn area into a common chamber, and 1 of these 2 also had an enlarged vestibule bilaterally. All had normal-appearing semicircular canals, and in all of the children, the deformity was bilateral and symmetric.

The hearing of all 5 children eventually progressed to the profound range of impairment prior to the time of implantation. All children met the audiologic criteria for inclusion in the clinical trial of the Clarion, consisting of a profound, bilateral sensorineural hearing loss (pure tone average ≥ 90 dB hearing level [HL]) and a score of 0% on the Phonetically Balanced-Kindergarten (PB-K) test.[17] However, all children had documented evidence of better hearing earlier in life, as shown in Table 3. Four of the 5 children suffered significant progression of hearing loss following trauma (baseball bat to head, fall on ice, fall, swimming pool diving).

Patients were evaluated preoperatively with hearing aids and at 3, 6, 12, and 18 months after initial implant stimulation on a battery of speech perception tests. In this report, performance on 2 open-set word tests, the PB-K test and the Glendonald Auditory Screening Procedure (GASP),[18] will be presented. The GASP test consists of 12 words of different syllable number and/or stress pattern. The more difficult PB-K test consists of monosyllabic words that are phonetically balanced words taken from the vocabulary of 5-year-old children with normal hearing. Half-lists of 25 words were used in the study. Recognition of sentences in an open-set format was assessed with the Common Phrases test[19] in the 4 older children (patients 1, 3, 4, and 5) and with the Mr Potato Head Task[20] in the younger child (patient 2). The Common Phrases test consists of simple phrases and sentences that the child must repeat. The Mr Potato Head Task assesses recognition of simple commands and actions. Testing was performed live-voice with auditory cues only.

RESULTS

All children had uneventful surgical procedures without perilymphatic gushers. All were discharged the morning after surgery, experienced no postoper-

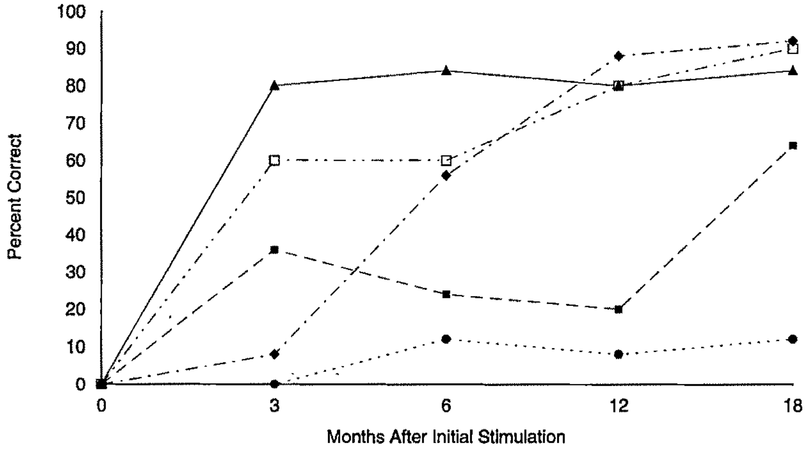


Fig 2. Percent correct scores for sentences as function of time after implantation. Common Phrases test was used with 4 older children, and Mr Potato Head Task was used with youngest child. Dark squares — patient 1; light squares — patient 2; diamonds — patient 3; circles — patient 4; triangles — patient 5.

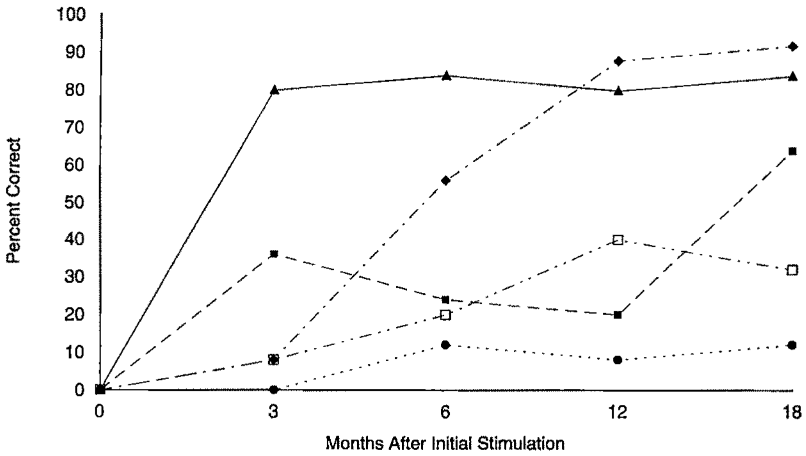


Fig 3. Percent correct scores for Phonetically Balanced-Kindergarten test as function of time after implantation. Dark squares — patient 1; light squares — patient 2; diamonds — patient 3; circles — patient 4; triangles — patient 5.

ative wound infections, and had their devices activated 3 to 5 weeks following surgery. Patient 5 developed 48 hours of nausea, vomiting, and vertigo 1 week after surgery that suddenly resolved without treatment and never returned (follow-up 31 months). Patient 2 experienced balance difficulty during the first 10 days after surgery, but gradually returned to normal. All children were programmed with the Continuous Interleaved Sampler speech processing strategy.

Figures 1-3 illustrate the results of the children over time on the open-set tests. Not every child had every test at every interval, due to time constraints. The trends for immediate improvement at the 3-month test interval, with further improvement at each subsequent interval, are evident from the slopes of the graphs, although the rates of improvement varied among the individuals. Sometimes, the greatest improvement was noted at a single test interval, for example, 3 months for patient 5 and 6 months for patient 3. For the others, it was more steady and progressive. There was a trend for continued improvement at the 18-month interval.

DISCUSSION

Although a perilymphatic gusher is a surgical risk in all patients with labyrinthine abnormalities, no gushers occurred in any of these 5 patients with large vestibular aqueducts (2 with Mondini-type cochlear abnormalities). This experience suggests that perilymphatic gushers may not be common with the LVAS syndrome.

The substantial and relatively rapid improvement in open-set speech recognition by these patients might reflect the progressive nature of their hearing loss and the fact that they had usable hearing prior to the onset of profound deafness. Schmidt[3] has reported a diminished number of viable auditory neurons in the presence of LVAS, which is inconsistent with the good results in these children. Furthermore, Schmidt found reduction of neuronal populations in newborns with Mondini dysplasia, as well as in adults, indicating that congenital absence of neurons as well as secondary neuronal degeneration affects the number of neurons available for electrical stimulation. Because the duration of profound deafness was relatively short for most of the children here, secondary auditory nerve degeneration is unlikely to be a significant factor. What is not known is whether the 2 children with Mondini deformities performed well because they had normal numbers of auditory neurons, or whether they succeeded in spite of a significantly reduced neuronal population.

CONCLUSIONS

The Clarion multichannel cochlear implant is both relatively safe and effective for children with enlarged vestibular aqueducts. Postimplant auditory recognition results are excellent in children who have the Mondini cochlear deformity, characterized by a normal basal cochlear turn and a confluent apex. Moreover, substantial improvement occurs in open-set speech recognition abilities after relatively limited implant experience. Therefore, implantation in these children should be considered as soon as it is apparent that recovery of hearing cannot be reasonably expected.

REFERENCES

1. Phelps PD. Cochlear implants for congenital deformities. J Laryngol Otol 1992;106:967-70.

2. Mondini C. Anatomica surdi nati sectio. De Bononiensi Scientarium et Artium Instituto atque Academia Commenarii. Banoniae 1791;7:419.

3. Schmidt JM. Cochlear neuronal populations in developmental defects of the inner ear: implications for cochlear implantation. Acta Otolaryngol (Stockh) 1985;99:14-20.

4. Valvassori GE, Clemis JD. Abnormal vestibular aqueduct in cochleovestibular disorders. Adv Otorhinolaryngol 1978;

24:100-5.

5. Valvassori GE, Clemis JD. The large vestibular aqueduct syndrome. Laryngoscope 1978;88:723-8.

6. Illum P. The Mondini type of cochlear malformation. Arch Otolaryngol 1972;96:305-11.

7. Jackler RK, De La Cruz A. The large vestibular aqueduct syndrome. Laryngoscope 1989;99:1238-42.

8. Levinson MJ, Parisier SC, Jacobs M, Edelstein DR. The large vestibular aqueduct syndrome in children. Arch Otolaryngol Head Neck Surg 1989;115:54-8.

9. Okumura T, Takahashi H, Honjo I, Takagi A, Mitamura K. Sensorineural hearing loss in patients with large vestibular aqueduct. Laryngoscope 1995;105:289-93.

10. Zalzal GH, Tomaski SM, Vezina LG, Bjornsti P, Grundfast K. Enlarged vestibular aqueduct and sensorineural hearing loss in children. Arch Otolaryngol Head Neck Surg 1995;121: 23-8.

11. Miyamoto RT, McConkey Robbins AJ, Myres WA, Pope ML. Cochlear implantation in the Mondini inner ear malformation. Am J Otol 1986;7:258-61.

12. Silverstein H, Smouha E, Morgan N. Multichannel cochlear implantation in a patient with bilateral Mondini deformities. Am J Otol 1988;9:451-5.

13. Molter DW, Pate BR Jr, McElveen JT Jr. Cochlear implantation in the congenitally malformed ear. Otolaryngol Head Neck Surg 1993;108:174-7.

14. Tucci DL, Telian SA, Zimmerman-Phillips S, Zwolan TA, Kileny PR. Cochlear implantation in patients with cochlear malformations. Arch Otolaryngol Head Neck Surg 1995;121: 833-8.

15. Slattery WH, Luxford WM. Cochlear implantation in the congenital malformed cochlea. Laryngoscope 1995;105:1184-7.

16. Aschendorff A, Marangos N, Laszig R. Large vestibular aqueduct syndrome and its implication for cochlear implant surgery. Am J Otol 1997;18(suppl 6):S57.

17. Haskins H. A phonetically balanced test of speech discrimination for children [Thesis]. Evanston, Ill: Northwestern University, 1949.

18. Erber NP. Auditory training. Washington, DC: Alexander Graham Bell Association for the Deaf, 1982.

19. Robbins AM, Renshaw JJ, Osberger MJ. Common Phrases Test. Indianapolis, Ind: Indiana University School of Medicine, 1988.

20. Robbins AM. Mr Potato Head Task. Indianapolis, Ind: Indiana University School of Medicine, 1993.

Ann Otol Rhinol Laryngol 108:1999

COCHLEAR IMPLANTATION IN CHILDREN UNDER THE AGE OF TWO: THE MHH EXPERIENCE WITH THE CLARION® COCHLEAR IMPLANT

THOMAS LENARZ, MD, PHD
ANKA LESINSKI-SCHIEDAT, MD
SABINE VON DER HAAR-HEISE
ANGELIKA ILLG
BODO BERTRAM
ROLF D. BATTMER, PHD
HANNOVER, GERMANY

This paper examines reports on the selection criteria, the surgical procedure; and the postoperative performance for children under the age of 2 implanted with the CLARION® Multi-Strategy™ Cochlear Implant (1.2 device). Eighteen children have been implanted since 1996 with a mean age at implantation of 18 months (range 11 to 23 months). All children were selected by means of a standardized preoperative diagnostic protocol. The surgical procedure used in older children was modified depending on the head and mastoid size, skull thickness, and recurrent otitis media. Auditory perception was tested prior to as well as 3, 6, 12, and 18 months following implantation by means of a standardized age-adapted test protocol. The electrode array was inserted without difficulty in all cases, with no complications to date. On average, auditory performance improved over time up to 18 months after implantation. Closed-set test scores increased by 25% to 55% in 18 months. Open-set test scores began to show improvement between 6 and 12 months postoperatively. Overall, our experience indicates that cochlear implantation in children under the age of 2 is relatively safe and reliable. The Clarion 1.2 device surgery can be performed without complications. Auditory performance results support the effectiveness of early implantation.

KEY WORDS — cochlear implantation, very young children.

INTRODUCTION

Cochlear implantation has proven to be an effective treatment for congenital and acquired deafness in children implanted after age 2 years. However, several studies indicate that results are better in children under the age of 4 than in children implanted at older ages.[1-4] Some of these children can achieve close to normal speech perception and production, as well as normal language development, when adequate educational and parental support is provided.[5] For these reasons, implantation in very young children below the age of 2 is desirable. However, there are several major issues of concern when considering implantation of very young children.[6]

1. Do the diagnostic tools currently available allow precise assessment of severe-to-profound bilateral deafness and/or usable residual hearing?[7]

2. Does head growth and recurrent otitis media, which is common in this age group, compromise the safety of cochlear implantation at this age?[8,9]

3. Are special surgical procedures necessary, and do they increase the complication rate for cochlear implantation at this age?[6]

4. Speech processor fitting at this age may prove more difficult, and age-related training programs may not be available.

5. Does early implantation provide results that outweigh any additional risks?

Since 1988, more than 700 children have been implanted at the Medical University of Hannover (Medizinische Hochschule Hannover; MHH). Sixty-one of the children were under the age of 2, 18 of whom received a CLARION® Multi-Strategy™ Cochlear Implant (1.2 device). This paper reports on the Hannover experience with preoperative assessment, surgical procedure, postoperative rehabilitation, performance data, and complications in the 18 Clarion children.

METHODS

Patients. Eighteen children under the age of 2 received a Clarion 1.2 cochlear implant. At the time of data analysis, they had been wearing the implant for at least 3 months (mean 11 months, range 3 to 24 months). The mean age at implantation was 18 months (range 11 to 23 months), the average duration of deafness was 6 months (range 0 to 12 months), and the mean age at diagnosis was 7 months. Hearing loss causes were congenital (n = 10), meningitis (n = 2), infection (n = 5), and ototoxicity (n = 1). All children underwent the standardized preoperative diagnostic protocol (Table 1). In addition, 2 children had CHARGE association, and 4 showed delayed motor system development or hypotonia.

Behavioral Testing. Preoperative speech perception and production skills were tested with a special

---

From the Department of Otolaryngology, Medizinische Hochschule Hannover (Lenarz, Lesinski-Schiedat, von der Haar-Heise, Illg, Battmer), and Children's Implant Center (Bertram), Hannover, Germany.

CORRESPONDENCE — Thomas Lenarz, MD, PhD, Dept of Otolaryngology, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.

TABLE 1. PREOPERATIVE DIAGNOSTIC PROTOCOL

Medical history and pediatric examination
Otoscopy
Acoustic reflexes and behavioral audiometry
Objective audiometry (auditory brain stem response, otoacoustic emissions, electrocochleography)*
Evoked auditory brain stem response*
Imaging (high-resolution computed tomography, magnetic resonance imaging)*
Ear inspection with ear paracentesis; ventilation tubes if necessary*
Pedagogic evaluation: status of speech and language development, overall development, cognitive abilities
Neuropediatric examination: additional handicaps

*Under general anesthetic.

TABLE 2. TEST BATTERY FOR AUDITORY PERCEPTION

Closed-set tests
TAPS (Test of Auditory Perception and Speech) pattern perception[10]
Two-syllable word recognition[11]
Monosyllable word recognition[11]
Minimal Pairs test[12]
Open-set tests
TAPS word recognition[10]
Monosyllable word recognition[11]
GASP test (Glendonald Auditory Screening Procedure Test)[13]
Mr Potato Head Task[14]
Questionnaires
MAIS (Meaningful Auditory Integration Scale)[15]
MUSS (Meaningful Use of Speech Scale)[16]

age-adapted test battery equivalent to the one used for the Clarion children's clinical trial in the United States.[10-14] The tests were adapted to the German language. They consisted of a set of closed-set materials, a set of open-set materials, and parent report scales (Table 2[10-16]). The same tests were administered at 3, 6, 12, 18, and 24 months after implantation.

At the time of diagnosis, all children were fitted with hearing aids and audioverbal education was begun or continued. In each case, a preimplant observation period lasted at least 6 months. If no or only minimal development was seen in auditory perception and speech and language after repeated testing, the child was classified as suitable for implantation. In cases of postmeningitic deafness, implantation was performed even before the end of this period of observation if any sign of obliteration of the cochlea was demonstrated by magnetic resonance imaging scans, repeated every 4 to 8 weeks.

Surgical Technique. A procedure similar to that performed in older children and adults was used. It was adapted to the age-specific risks of head growth, recurrent otitis media, thickness and size of skull, and the specific anatomy of the temporal bone.

The following procedures were used.[17]

1. An enlarged supra-aural skin incision was made at a distance of 2 cm to the implant site.

2. An inferiorly based monolayer skin-muscle flap was created with adequate exposure of the mastoid. This flap has an excellent blood supply via the occipital artery.

3. A complete mastoidectomy was performed with drill-out of nonaerated areas to gain maximum space for placement of the electrode lead. A cortical bone overhang was preserved to protect this lead.

4. A bone bed for the implant was created in a flat area posterior-superior to the mastoid cavity at a distance of approximately 1 cm. The dura had to be exposed at the edges of the bed due to a skull thickness of only 2 to 3 mm. In the center, a bone island was preserved, which later allowed for regrowth of bone. Bone holes for crossing sutures were placed on both sides of the implant. The implant then could be tied down by impressing the dura to provide secure placement and to avoid any movement or protrusion.[18]

5. A cortical bone bridge was preserved between the implant bed and the mastoid to provide protection for the fantail and the initial part of the electrode lead (Fig 1).

6. A posterior tympanotomy was performed with special attention to the more lateral course of the facial nerve and the small superior-inferior dimension of the mastoid. The chorda tympani could be preserved in most cases. Facial nerve integrity was monitored in cases of inner ear malformation.

7. The cochleostomy was started anterior to the round window niche. It was enlarged, enclosing the round window up to a diameter of 2 mm. Special attention was given to the basilar membrane.

8. The electrode was inserted with the metal insertion tube. The electrode was detached from the insertion tool, and the cochleostomy was sealed with connective tissue. The implant was tied down to the dura with nonresorbable sutures.

9. The integrity of the implant was tested via telemetry using a portable cochlear implant tester. In addition, the stapedius muscle reflex could be elicited and directly observed through the microscope. The threshold of the reflex is related to the most comfortable (M) level and can be used for the first postop-

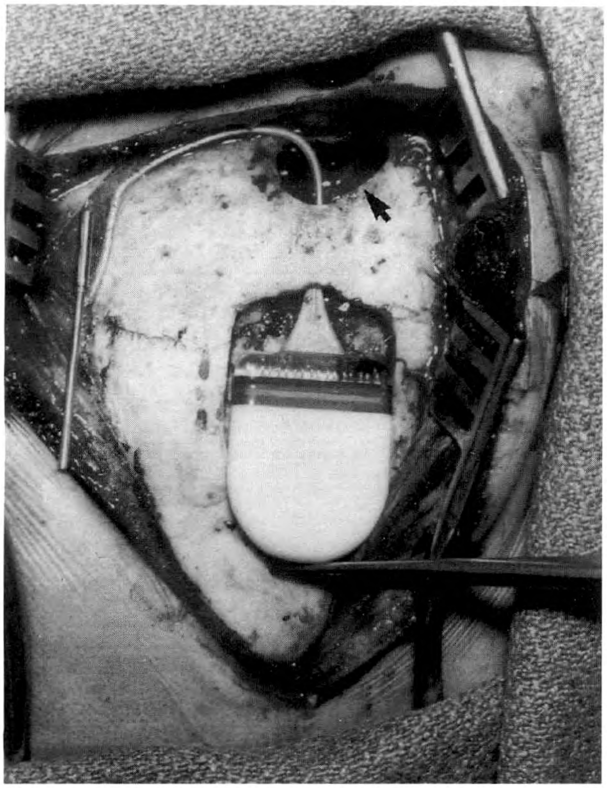


Fig 1. Clarion 1.2 implant positioned in bone bed with electrode lead going to mastoid.

erative fitting. However, a specific regimen for anesthesia is required.[19]

10. The wound was closed without drainage. A pressure dressing was applied for 3 days, and the stitches were removed after 10 days.

Postoperative Fitting, Audioverbal Training, and Speech Perception Testing. Four to 5 weeks after surgery, the children were admitted with a parent to the Children's Implant Center (CIC) for 1 week. Speech processor fitting was performed by a step-by-step activation of electrodes from apex to base. The M levels were based upon the intraoperative stapedius reflex thresholds. The threshold (T) levels were estimated from the child's behavioral responses to increasing stimulus levels and continuously adjusted to more appropriate, ie, lower, levels. Age-related audioverbal training was begun, which included participation by parents. The training sessions (pretraining, speech processor fitting, hearing and speech education, development of language skills, cognitive education, multisensory training, motor training, music education, and play groups) were continued at CIC together with repeated performance testing at MHH at intervals of 3 months up to 2 years. Three-month data are available for all children, and 18-month data are available for a small number of children.[20]

TABLE 3. COMPLICATIONS IN COCHLEAR IMPLANTATION IN VERY YOUNG CHILDREN

	No. of Cases (N = 18)
Device failure	0
Wound infection	1
Electrode misplacement	0
Facial nerve injury	0
Chorda tympani injury	2
Otitis media	7

RESULTS

The preoperative diagnostic protocol was effective in diagnosing hearing loss in all children. Early detection of deafness was achieved either by neonatal auditory screening or testing immediately after the onset of acquired hearing loss. Objective tests typically showed no otoacoustic emissions and no electrocochleographic response or evoked auditory brain stem response (EABR). Electrical stimulation at the promontory with a needle electrode elicited EABRs in only 11 of the 18 cases. Behaviorally, the children showed either no reaction to amplification or no benefit in speech perception and production after at least 6 months.

The surgical procedure could be performed and completed safely in all cases. The chorda tympani had to be sacrificed in 2 cases due to the narrow space at the posterior tympanotomy and to avoid any damage of the facial nerve. Only minor complications occurred (Table 3). To date, no device failures have occurred.

All children were fitted with the Continuous Interleaved Sampler (CIS) strategy. Because a monopolar stimulation mode was used, the fitting could be performed quickly. The estimation of M levels from stapedius reflex thresholds was helpful and was used in 14 of the 18 children. The stapedius reflex could not be observed in 2 children during surgery. In 2 other cases, the estimated levels were too low to elicit a behavioral response. The T levels could always be estimated from the child's reaction to the stimuli and could be reduced over subsequent days, thereby increasing the dynamic range. In some cases, the headpiece attachment at the skull had to be supported with an open ear-mold with cable fixation to provide stress relief. The speech processor was supported by a special tag worn by a belt around the neck and chest. All children wear their speech processor every day for 10 to 15 hours.

Speech perception results could not be obtained from all children at all test intervals. There were several reasons, including a lack of cooperation by ei-

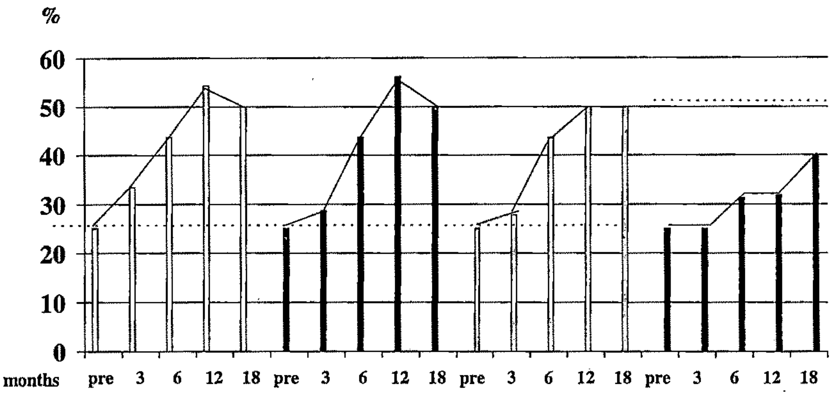


Fig 2. Closed-set auditory perception test results. Mean preoperative and postoperative test scores over time. Chance-level scores are indicated by dotted line. Four tests are, left to right, Pattern Perception, 2-syllable words, monosyllable words, and Minimal Pairs.

ther the child or parents, limited intellectual and behavioral abilities, and insufficient speech-production development.

In general, the auditory performance in all children improved over time up to 12 months. On average, closed-set test scores exceeded chance levels after 6 months and showed a steady and continuous improvement over time (Fig 2 and Table 4). The greatest increases seen were in Pattern Perception and 2-syllable word recognition. The increase was smaller for the monosyllable word recognition test, and the smallest change was found for the Minimal Pairs test. This pattern reflects the relative difficulty of the tests.

For some tests, the scores after 18 months were lower than those after 12 months. However, the number of children tested at 18 months after implantation was very small. Consequently, the test results may be confounded by the small number of individuals tested.

Open-set test scores also increased over time postimplantation, but with a delay of 6 months (Fig 3 and Table 5). Scores above chance were first observed 12 months after implantation, with further improvement at 18 months. The smallest gain was seen in the GASP[13] results, whereas the greatest improvement was seen in the TAPS[10] scores. Again, this pattern reflects the different levels of test complexity and difficulty.

DISCUSSION

Cochlear implantation in children under the age of 2 with the Clarion 1.2 system was performed successfully in 18 children at MHH. Based upon extensive and long-standing experience at this department with pediatric cochlear implantation, it was possible to develop a specific age-adapted protocol for careful selection of candidates, a feasible surgical procedure, and effective postoperative rehabilitation.[21]

A fundamental aspect of early implantation is accurate identification of hearing loss. Early identification allows early hearing aid fitting and audioverbal training to be initiated, and provides sufficient time for observation before implant candidacy is determined. Thus, neonatal screening and confirmation of hearing loss by objective audiometric tests is essential.[22,23] In cases of postmeningitic deafness, immediate auditory evaluation is mandatory to establish the diagnosis before cochlear obliteration.[24]

Our experience shows the importance of objective audiometric tests for assessment of hearing in very young children. Even when the tests were not able to rule out any residual hearing, especially at the low frequencies, our data revealed a good correlation between the results of these objective audiometric tests and the behavioral data obtained during the preimplant observation period. If objective tests elicited no auditory responses, there was a high probability that any residual hearing would not be beneficial for speech and language development, even under aided conditions.

The 6-month observation period also provided time for preparing the family and child for implan-

TABLE 4. RESULTS OF AUDITORY PERCEPTION TESTS (CLOSED SET)

	Pattern Perception				*Two-Syllable*				*Monosyllable*				*Minimal Pairs*			
Time	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*
Preop	12	25	25	25	12	25	25	25	12	25	25	25	12	25	25	25
Postop 3 mo	9	33	25	100	9	29	25	58	9	28	25	50	9	25	25	25
Postop 6 mo	4	44	25	100	4	44	25	100	4	44	25	100	4	31	25	50
Postop 12 mo	4	54	17	100	4	56	25	100	4	50	25	100	4	32	25	52
Postop 18 mo	3	50	25	100	3	50	25	100	3	50	25	100	3	40	25	70

Data are % correct.

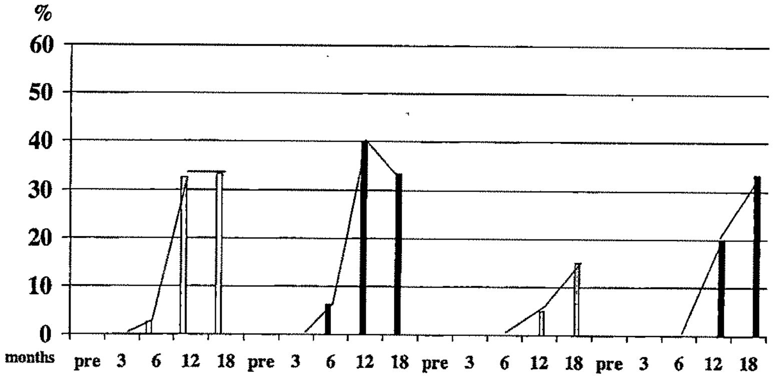


Fig 3. Open-set auditory perception test scores. Mean preoperative and postoperative test scores over time. Chance-level scores are indicated by dotted line. Four tests are, left to right, TAPS, monosyllable words, GASP, and Mr Potato Head.

tation. An audioverbal training program was established, and any additional handicaps were assessed.[25] Then, the decision to implant could be made clearly with the full support of the parents and the institutions involved. The involvement of this team is of great importance in providing the lifelong support required after implantation and in managing nonrealistic expectations.[26]

The surgical experience shows that the implantation of the Clarion 1.2 system can be performed reliably and relatively safely in young children, with few and minor complications. Specific modifications of the surgical procedure are necessary to handle the age-related risks and safety issues properly.[27] Once healing was completed, no increased risk for extraction of the electrode due to head growth, labyrinthitis, or meningitis due to the higher frequency of otitis media or facial nerve damage was observed.[8] The mastoidectomy seems to be a good procedure to prevent mastoiditis. No complications from dura exposure have been observed, and skull growth is not influenced.

The postoperative speech processor fitting and audioverbal training also are possible and successful. However, it is important to have experienced clinicians to minimize the potential for device rejection.[20,28]

Speech perception results show a constant improvement over time. After 6 to 12 months, suprasegmental and prosodic elements of speech are detected and produced. Everyday environmental sounds can be differentiated. Open-set speech understanding improves in the second year after implantation. In addition to improved test results, clinical observations indicate better voice control and improved interaction with family members. The child's behavior changes toward auditory attention. Speech production also improves, as indicated by the ability to form monosyllabic words.[29]

The MMH experience supports the concept that early implantation minimizes the effects of auditory deprivation on the development of the auditory system.[30,31] At this age, electrical stimulation provides the necessary information to the auditory system at the critical period for speech development and language acquisition.[1,32] So far, our results are promising, although long-term follow-up of these children is necessary to evaluate the final outcome in terms of speech and language development, psychosocial development, and social integration. In particular, it will be important to compare results to those in other age groups, especially children who are older at the time of implantation.[33] Two-year postimplant data from MHH show that performance is clearly age-dependent in that speech perception scores in older children (over 6 years) plateau.[17] The data reported here suggest that early implantation, soon after the correct diagnosis has been made, provides children with a good chance to develop near-normal speech and language.[5,34] Finally, the Clarion 1.2 implant is suitable for this age group and has proven to be relatively safe and effective for auditory rehabilitation.

TABLE 5. RESULTS OF AUDITORY PERCEPTION TESTS (OPEN SET)

	TAPS				*Monosyllable*				*GASP*				*Mr Potato Head*			
Time	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*	*No.*	*Mean*	*Min*	*Max*
Preop	11	0	0	0	12	0	0	0	12	0	0	0	12	0	0	0
Postop 3 mo	9	0	0	0	9	0	0	0	9	0	0	0	9	0	0	0
Postop 6 mo	4	3	0	10	4	6	0	25	4	0	0	0	4	0	0	0
Postop 12 mo	4	33	0	100	4	40	0	100	4	5	0	20	4	20	0	80
Postop 18 mo	3	33	0	100	3	33	0	100	3	15	0	45	3	33	0	100

Data are % correct.

REFERENCES

1. Waltzman S, Cohen N, Gomolin R, Ozdamar S, Shapiro W, Hoffman R. Effects of short-term deafness in young children implanted with the Nucleus cochlear prosthesis. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):341-2.

2. Lesinski A, Battmer RD, Bertram B, Lenarz T. Appropriate age for cochlear implantation in children — experiences since 1986 with 370 children. Adv Otorhinolaryngol 1997;52: 214-7.

3. Lesinski A, von der Haar-Heise S, Battmer RD, Büchner A, Goldring JE, Lenarz T. Performance of German-speaking children with the CLARION Cochlear Implant. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

4. Lesinski-Schiedat A, Illg A, Rost U, Issing PR, Lenarz T. Zwei-Jahres-Ergebnisse einer sprachtestgestützten Verlaufsbeobachtung bei Kindern mit Cochlear Implant. 69. Jahrestagung der Dt. Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie, Hannover/Germany, May 22-24, 1998.

5. Szagun G. Some aspects of language development in normal-hearing children and children with cochlear implants. Am J Otol 1997;18:131-4.

6. Lloyd RV, Gibbin KB, O'Donoghue GM. Pediatric cochlear implants. Surgical aspects: the Nottingham pediatric cochlear implant programme. Rev Laryngol Otol Rhinol (Bord) 1995;116:85-7.

7. Lenarz T, Bertram B, Lehnhardt E. Cochlear Implant bei Kindern. Stuttgart, Germany: Thieme, 1994.

8. Dahm MC, Shepherd RK, Clark GM. The postnatal growth of the temporal bone and its implications for cochlear implantation in children. Acta Otolaryngol Suppl (Stockh) 1993 (suppl 505).

9. Burton MJ, Shepherd RK, Xu SA, Franz BK, Clark GM. Cochlear implantation in young children: histological studies on head growth, leadwire design and electrode fixation in the monkey model. Laryngoscope 1994;104:167-75.

10. Tests of auditory perception of speech (TAPS) for children (German version). Basel, Switzerland: Cochlear AG, 1992.

11. Biesalski PH, Leitner E, Leitner A, Gangel D. Der mainzer kindersprachtest. Sprachaudiometric im Vorschaulter. HNO 1974;22:161-2.

12. Schafer J. Bidwortserie zue Lautagnosierufund un zur Schulung des phonematischen Gehors. Die Sprachbeilarbeit, Heft 1973;3:83-9.

13. Erber N. Auditory training. Washington, DC: Alexander Graham Bell Association, 1982.

14. Robbins AM. Mr Potato Head Task. Indianapolis, Ind: Indiana University School of Medicine, 1988.

15. Robbins AM, Renshaw JJ, Berry SW. Evaluating meaningful auditory integration in profoundly hearing impaired children. Am J Otol 1991;12(suppl):144-50.

16. Robbins AM, Osberger MJ. Meaningful Use of Speech Scale (MUSS). Indianapolis, Ind: Indiana University School of Medicine, 1990.

17. Lenarz T, Battmer RD, Bertram B. Cochlear implantation in children under the age of two. Presented at the 7th Symposium on Cochlear Implants in Children, Iowa City, Iowa, June 4-7, 1998.

18. Cohen NL. Medical and surgical considerations in cochlear implants for children. Presented at the Third European Symposium on Pediatric Cochlear Implantation, Hannover, Germany, June 6-8, 1996.

19. Gnadeberg D, Battmer RD, Lüllwitz E, Laszig R, Dybus U, Lenarz T. Der Einfluß der Narkose auf den intraoperativ elektrisch ausgelösten Stapediusreflex. Laryngorhinootologie 1994;73:132-5.

20. Battmer RD, Gnadeberg D, Allum-Mecklenburg DJ, Lenarz T. Algorithmic representation of common ground programming in children with the Nucleus device. Adv Otorhinolaryngol 1995;50:83-90.

21. Bertram B. Importance of auditory-verbal education and parents' participation after cochlear implantation of very young children. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):97-100.

22. National Institutes of Health. Cochlear implants in adults and children. JAMA 1995;274:1955-61.

23. Reuter G, Bördgen F, Dressler F, et al. Neugeborenen-Hörscreening mit dem automatisierten Meßgerät Echosensor für akustische Emissionen: eine vergleichende Untersuchung. HNO (in press).

24. Hartrampf R, Weber B, Dahm MC, Lenarz T. Management of obliteration of the cochlea in cochlear implantation. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):416-8.

25. Lesinski A, Hartrampf R, Dahm MC, Bertram B, Lenarz T. Cochlear implantation in a population of multihandicapped children. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):332-4.

26. Bertram B. Cochlear implantation at an early age: first experience. Presentation at British Cochlear Implant Group, Lancaster, September 3-4, 1998.

27. Mack KF, Müller J, Helms J. Dimensions of the temporal bone in small children in relation to the cochlear implant — analysis of CT scans. Adv Otorhinolaryngol 1997;52:57-9.

28. Brown CJ, Abbas PJ, Fryauf-Bertschy H, Kelsay D, Gantz BJ. Intraoperative and postoperative electrically evoked auditory brain stem responses in Nucleus cochlear implant users: implications for the fitting process. Ear Hear 1994;15:168-76.

29. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Open-set speech perception in congenitally deaf children using cochlear implants. Am J Otol 1997; 18:342-9.

30. Leake PA, Snyder RL, Hrade GT, Rebscher SJ. Consequences of chronic extracochlear electrical stimulation in neonatally deafened cats. Hear Res 1995;82:65-80.

31. Reuter G, Cords SM, Issing PR, Keller P, Lenarz T. Intracochlear, electrical, multichannel stimulation effects on the development of auditory system in neonatally deafened kittens. Am J Otol 1997;18(suppl):13-4.

32. Schönweiler R. Eine Untersuchung an 1300 Kindern zur Inzidenz und Therapie von Hörstörungen bei kindlichen Sprachstörungen. Laryngorhinootologie 1992;71:637-43.

33. Illg A, von der Haar-Heise S, Battmer RD, Lenarz T. Development in cochlear implant children and adolescents aged 7 to 18 years. Presented at the 4th European Symposium on Paediatric Cochlear Implantation, s'Hertogenbosch, the Netherlands, June 14-17, 1998.

34. Robbins AM, Osberger MJ, Miyamoto RT, Kessler KS. Language development in young children with cochlear implants. Adv Otorhinolaryngol 1995;50:160-6.

Ann Otol Rhinol Laryngol 108:1999

RELATIONSHIP BETWEEN EABR THRESHOLDS AND LEVELS USED TO PROGRAM THE CLARION® SPEECH PROCESSOR

CAROLYN J. BROWN, PHD
MICHELLE L. HUGHES, MA
SUSAN M. LOPEZ, MA
PAUL J. ABBAS, PHD
IOWA CITY, IOWA

The purpose of this study was 1) to describe the relationship between electrically evoked auditory brain stem response (EABR) thresholds and the behavioral measures needed to program the speech processor of the CLARION® Multi-Strategy™ Cochlear Implant, and 2) to determine whether the relationship between EABR threshold and the behavioral levels used to program the Clarion device was correlated with the temporal integration abilities of these subjects. The EABR thresholds, psychophysical thresholds, and the Clarion speech processor programming levels were recorded from 29 postlingually deafened adults. The mean EABR thresholds approximated most comfortable levels (M levels) for the programming stimulus. However, intrasubject variability was substantial. Significant intrasubject variability in temporal integration also was observed. Correlations were found between the ability of a cochlear implant user to perform temporal integration and the relationship between his or her EABR threshold and the threshold for the programming stimulus.

KEY WORDS — auditory evoked potential, cochlear implant, electrical stimulation.

INTRODUCTION

Cochlear implants have been available to postlingually deafened adults since the early 1980s and have been approved for use with children 2 years of age and older since 1990. Congenitally deaf children who receive their cochlear implants at a very young age are able to obtain higher postimplant speech recognition scores than do children implanted at a later age.[1-3] Currently, children as young as 18 months of age are eligible to receive a cochlear implant, and there have been anecdotal reports of individual children as young as 10 months of age receiving a multichannel cochlear implant.[4] It is possible that as experience with cochlear implants increases, the trend toward implanting younger children will continue. Additionally, the number of persons with multiple developmental delays who will be considered eligible to receive a cochlear implant may increase.

The task of programming the speech processor for young and/or multiply impaired populations can be difficult, because these individuals often have extremely limited expressive language skills. One solution to the problem of programming the speech processor for these individuals may be to use the electrically evoked auditory brain stem response (EABR). Its counterpart, the acoustically elicited auditory brain stem response, is a tool that has been used successfully for many years to predict behavioral thresholds for very young or difficult-to-test patients.[5]

The EABR thresholds have been shown to correlate fairly strongly with behavioral thresholds if the same stimulus is used to evoke both the physiologic and the behavioral responses.[6] A number of investigators have explored the extent to which EABR thresholds, recorded with a standard, relatively slow-rate stimulus, correlate with either the behavioral threshold or maximum comfort levels for the higher-frequency pulse train used to program the speech processor of the cochlear implant.[6-10] While the results of these studies have been somewhat varied, in general, a strong correlation between EABR threshold and behavioral threshold or maximum comfort level has not been found. Results obtained in our laboratory for persons using the Nucleus 22-channel cochlear implant show that mean EABR threshold corresponded to a level that was approximately two thirds of the way between behavioral threshold and maximum comfort level for the 250-Hz stimulus used to program the Nucleus speech processor.[6] Examination of the individual data, however, revealed considerable intrasubject variability, and we suggested that much of this variability could be attributed to differences in temporal integration across subjects.[6]

One goal of this study was to measure the relationship between EABR thresholds and the behavior-

---

From the Departments of Speech Pathology and Audiology (Brown, Abbas) and Otolaryngology–Head and Neck Surgery (all authors), University of Iowa, Iowa City, Iowa. Supported by research grant DC00242 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders; grant RR59 from the General Clinical Research Centers Program, National Institutes of Health; and the Iowa Lions Sight and Hearing Foundation.

CORRESPONDENCE — Carolyn J. Brown, PhD, Dept of Speech Pathology and Audiology, 119 WJSHC, University of Iowa, Iowa City, IA 52242-1012.

al measures needed to program the speech processor of the CLARION® Multi-Strategy™ Cochlear Implant. All of the studies referenced above have explored that relationship for patients who have received the Nucleus cochlear implant. However, to date, more than 3,500 persons worldwide have been implanted with the Clarion device. This number includes children as young as 18 months of age. There are many differences between the Nucleus and Clarion cochlear implant systems. For example, patients using the Nucleus cochlear implant are typically programmed in a bipolar stimulation mode, while the majority of patients who use the Clarion system use monopolar stimulation. Additionally, the Clarion speech processor is programmed by setting behavioral threshold (T level) and most comfortable levels (M level) for a stimulus that is often more than twice the frequency of the stimulus used to program the Nucleus speech processor. Given the difference in stimuli used to program the Clarion and Nucleus speech processors, one may expect that the relationship between EABR thresholds and the variables used to program the speech processor would be different for the 2 devices.

A second goal of this study was to measure temporal integration directly and to explore the relationship between temporal integration abilities of Clarion users and how well EABR thresholds correspond to behavioral thresholds. We have postulated that some of the intrasubject variability that we have observed with Nucleus cochlear implant users may be due to a difference in temporal integration across subjects.[6] Specifically, patients with poor temporal integration may show good agreement between EABR thresholds obtained with a relatively slow-rate stimulus and behavioral thresholds obtained with a higher-frequency stimulus. In contrast, patients with excellent temporal integration may show relatively larger differences between EABR thresholds measured with a slow stimulation rate and behavioral thresholds measured with a higher stimulation frequency.

METHODS

Subjects. Twenty-nine postlingually deafened adults participated in this study. All subjects received the Clarion cochlear implant between 1992 and 1995 at the University of Iowa Hospitals and Clinics and had been using their implant for at least 1 year at the time of data collection. In each case, full insertion of the intracochlear electrode array was achieved. All 29 subjects were programmed with the Continuous Interleaved Sampler (CIS) speech processing strategy in monopolar mode.

Data were collected in 3 different phases. Initially, behavioral measures used to program the speech processor were obtained by an audiologist experienced in programming the Clarion device. In addition to measuring T levels and M levels, uncomfortable levels (UCL) were measured. The M levels and UCLs were balanced across electrodes. Twelve subjects were programmed with stimulus durations of 150 microseconds (μs) per phase, and 17 subjects were programmed with 75–μs per phase stimulus durations. The pulse width used was based on patient performance and preference. Twenty-seven subjects used all 8 available intracochlear electrodes. Two subjects had problems with facial nerve stimulation or abnormal electrode function and preferred to use a program that included only 7 of the 8 intracochlear electrodes. With the Clarion programming software, the frequency of the programming stimulus varies depending on the number of active channels and the pulse width of the electrical stimulus preferred by the cochlear implant user. For the subjects participating in this study, the programming stimulus was a train of biphasic current pulses that ranged in frequency from approximately 416 Hz (for an 8-channel program that used 150–μs per phase pulse widths) to 934 Hz (for a 7-channel program that used 75–μs per phase pulse widths).

Electrophysiologic data were generally collected during a second 3-hour recording session. Psychophysical experiments were conducted during a third (and occasionally a fourth) session. Procedural details relative to each of these 3 phases of data collection are outlined below.

Electrophysiological Procedures. Stimuli for EABR recordings were generated with software (SCLIN, v2.0) developed by Advanced Bionics Corporation and delivered to the implant via the Clarion programming interface. Stimuli used to evoke the EABR consisted of a train of biphasic current pulses presented at a rate of 13.9 Hz. Stimulus polarity was alternated in order to reduce contamination of the evoked potential by stimulus artifact. Stimulus durations of either 75 or 150 μs per phase were used for evoked potential testing and were selected to match the pulse duration provided by the subject's processor.

During the electrophysiological recording sessions, subjects were seated in a recliner and asked to relax and watch closed-captioned videos. Surface recording electrodes were placed high on the forehead (positive), on the mastoid process contralateral to the implanted ear (reference), and on the mastoid process ipsilateral to the implanted ear (ground). A custom-constructed, ground-isolated, radio frequency (RF)–shielded amplifier with a gain of 10,000 preceded input to the averaging computer, which was

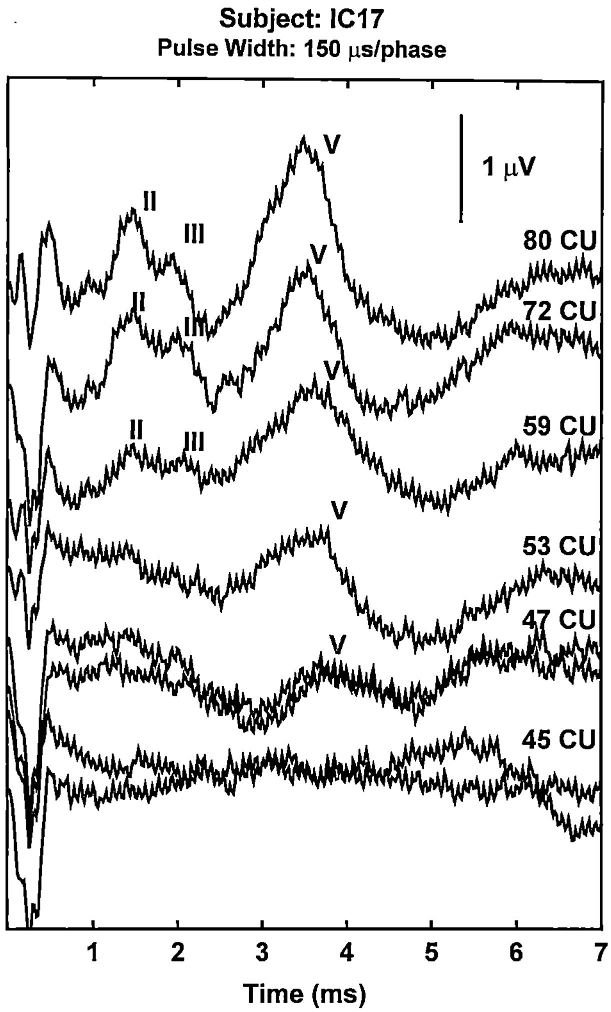


Fig 1. Evoked auditory brain stem responses (EABR) recorded for 6 stimulation levels for Clarion cochlear implant user (subject IC17). Stimulus is 150–microsecond per phase biphasic current pulse. Stimulation mode was monopolar, and stimulating electrode was medial electrode of electrode pair 1.

equipped with a 16-bit analog-to-digital converter and custom averaging software. Two or more EABR recordings of 1,000 sweeps each were obtained for each stimulation level. Artifact rejection was used to eliminate excessively noisy sweeps from the average. The EABR responses were recorded for a series of 4 or more stimulation levels spaced across the subjects' dynamic range. An EABR threshold was defined as the lowest stimulation level at which a replicable response could be identified visually.

The EABR thresholds were recorded for each subject with monopolar stimulation of the medial electrode of electrode pairs 1, 4, and 8. For 3 subjects, it was possible to record electrophysiological (and psychophysical) data from only 1 or 2 of these stimulating electrodes due to facial stimulation, problems with malfunctioning electrodes, or time constraints.

Psychophysical Procedures. A 2-alternative, forced-choice paradigm was used to estimate psychophysical thresholds for 3 different stimuli: a single biphasic current pulse (either 75 or 150 μs per phase) and a 250-millisecond (ms) burst of both 400- and 1,000-Hz biphasic pulse trains. Stimuli used for psychophysical testing were generated with custom software provided by Advanced Bionics Corporation and delivered to the subject via the original MS-DOS–based Clarion programming interface.

During testing, the subject was asked to watch a computer screen. Two 500-ms listening intervals marked with lighted boxes on a computer screen were presented, separated by approximately 300 ms. Initially, stimuli were presented at a comfortable level, and the listener was asked to select which interval contained the stimulus. The stimulus level was decreased in steps of 2 Clinical Units (CU; corresponding to approximately 0.6 dB) for every 3 correct responses. Following an incorrect response, the step size was halved and the stimulation level was increased until 3 correct responses were obtained. Feedback was provided and this adaptive procedure continued until 11 reversals were recorded. This procedure converges on a level at which 79% accurate identification is achieved. The threshold for each trial was defined as the geometric average (in programming units) of the last 4 reversals. The psychophysical threshold for each stimulus condition was defined as the average of 3 or more trials. A conversion table, supplied by Advanced Bionics, was used to convert CU to current in microamperes.

RESULTS

Figure 1 shows a series of EABR waveforms recorded for 1 subject for stimulation levels between 45 and 80 CU. At the highest stimulus level, wave V has a latency of 3.6 ms. As the stimulus level is decreased, the amplitude of wave V decreases and the latency increases slightly. The morphology of this response is similar to that of responses recorded previously from both Ineraid and Nucleus cochlear implant users.[6,11] For each subject, a series of EABR recordings were made and visual detection thresholds were identified. In Fig 1, the visual detection threshold for the EABR is 47 CU.

One of the primary goals of this study was to determine how EABR thresholds related to the variables used to program the Clarion speech processor (T and M levels). Figure 2 shows results from 3 Clarion cochlear implant users. For each subject, the stimulating electrode is plotted on the abscissa. The T and M levels are indicated with open circles and triangles, respectively; the UCL is plotted with open squares. The EABR thresholds are plotted with filled circles. Individual data from 3 subjects are shown to illus-

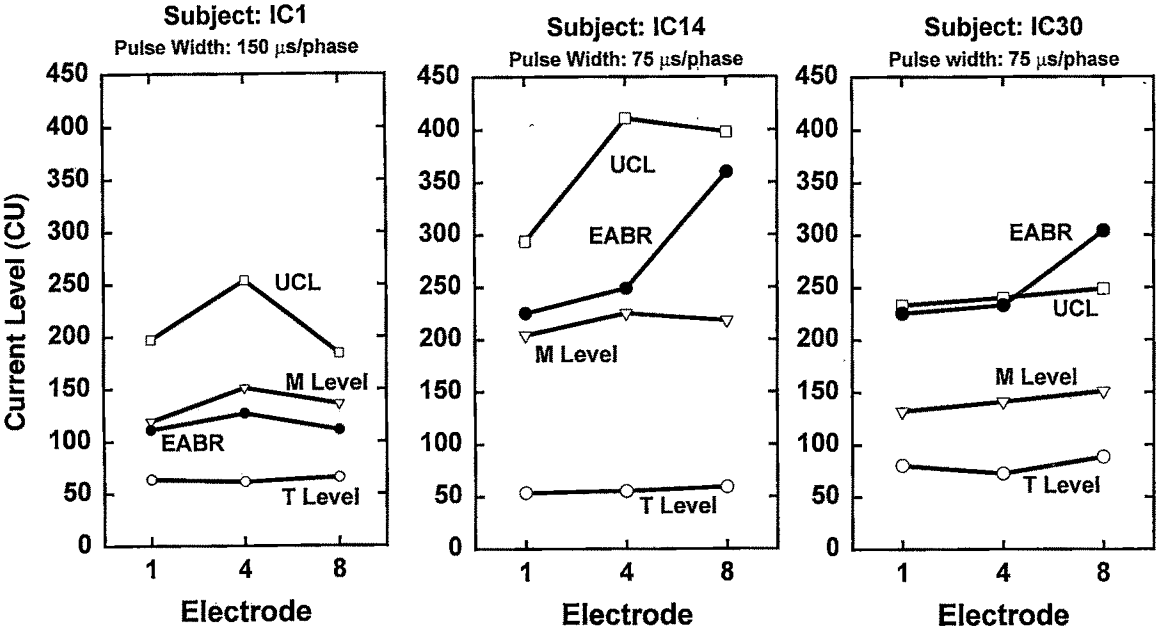


Fig 2. EABR thresholds and programming parameters for 3 Clarion cochlear implant users. For each subject, EABR thresholds for each of 3 stimulating electrodes obtained with 13.1-Hz stimulation rate are marked with filled circles. Behavioral T and M levels used to program speech processor are shown with open circles and triangles, respectively. Level at which programming stimulus became uncomfortable for each subject is indicated with open squares.

trate the cross-subject variability. For subject IC1, EABR thresholds were recorded at levels below the levels she identified as most comfortable. For subject IC14, whose data are shown in Fig 1, the EABR thresholds were recorded at levels above the subject's M levels but still within his dynamic range. Finally, for some subjects, such as subject IC30, whose data are shown in the right-hand panel of Fig 1, the EABR thresholds elicited with the slow stimulation rate were obtained at levels that approximated or occasionally exceeded levels judged to be uncomfortable for the programming stimulus.

Figure 3 shows a series of scatterplots that describe the relationship between EABR threshold and the stimulation levels used to program the Clarion speech processor. The left panel shows the relationship between the EABR threshold and behavioral T levels. The center panel shows the relationship between EABR threshold and M levels. These are the 2 levels used to program the Clarion speech processor. The right panel shows the relationship between EABR threshold and behavioral estimates of UCL. The solid line on each panel shows where the data would fall if the 2 measures were equal. The dotted

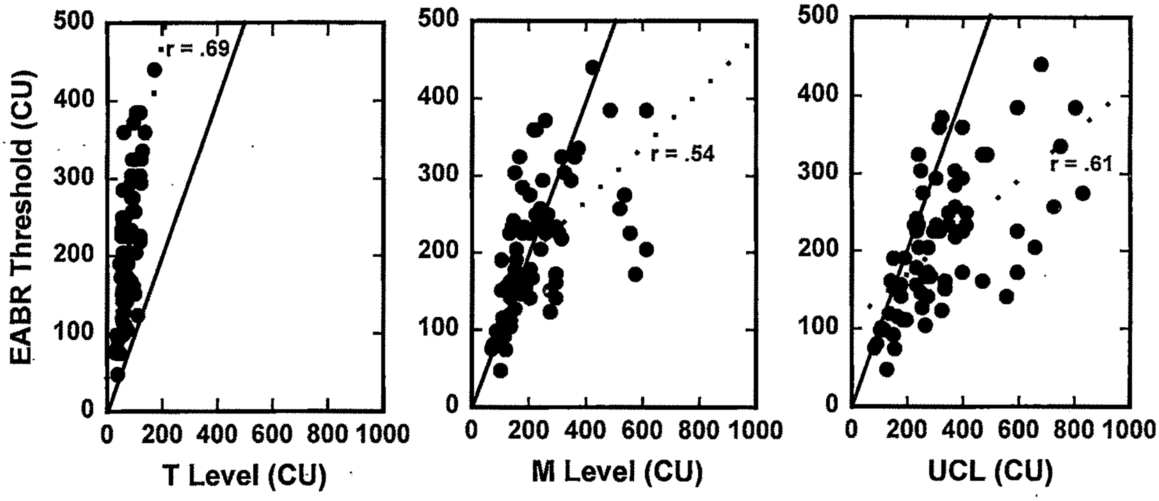


Fig 3. Correlations between EABR thresholds and behavioral T levels, M levels, and UCLs. Solid line on each Figure indicates point at which these 2 variables are equal. Dotted line indicates result of linear regression of data. CU — clinical units.

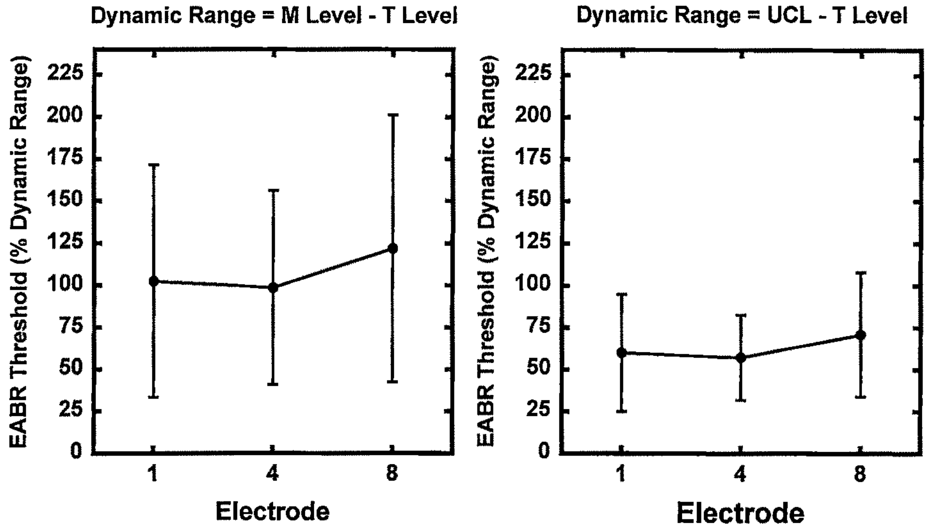


Fig 4. Mean EABR thresholds for each electrode plotted as percentage of subjects' dynamic range for programming stimulus. Error bars indicate ±1 standard deviation from mean. In left panel, dynamic range is defined as difference between behavioral threshold (T level) and most comfortable level (M level). In right panel, dynamic range is defined as difference between behavioral threshold (T level) and level at which programming stimulus became uncomfortable.

line on each panel is the result predicted by linear regression of the data.

These results indicate considerable cross-subject variability. Clearly, EABR thresholds are recorded from all subjects at levels that exceed the behavioral thresholds used to program the speech processor. For most subjects, EABR threshold is recorded at levels that approximate behavioral MCLs. However, in about half the cases, EABR thresholds actually exceed behavioral MCLs. In only a few cases do EABR thresholds exceed UCLs for the programming stimulus.

The data in Fig 3 illustrate the relationship between EABR threshold and the behavioral levels used to program the speech processor. In some instances, the EABR threshold exceeded MCL by as much as 100 to 150 CU. The significance of an error of that magnitude needs to be interpreted in light of the size of the subject's dynamic range. Figure 4 shows mean EABR threshold for each of the 3 electrodes tested. In this Figure, the EABR threshold is expressed as a percentage of the subject's dynamic range. In the left-hand panel, dynamic range has been defined as the difference between behavioral measures of threshold and most comfortable level. In the right panel of Fig 4, dynamic range is defined as the difference between behavioral measures of threshold and uncomfortable loudness level. Error bars indicate ±1 standard deviation from the mean. In the left panel, a value of 0 means the EABR threshold was equal to behavioral threshold and a value of 1 means the EABR threshold was equal to MCL. In the right panel, a value of 0 again means EABR threshold was equal to behavioral threshold and a value of 1 indicates that EABR threshold is equal to UCL. Clearly, there is considerable variability in the data. In general, however, EABR thresholds indicate a level that approximates MCL and lies just over halfway between the threshold and the UCL.

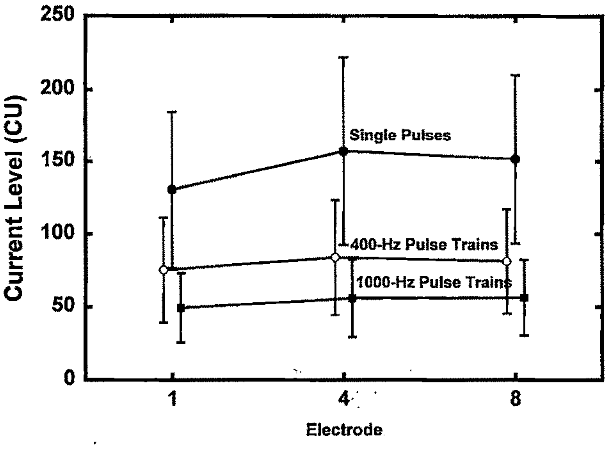


Fig 5. Psychophysical thresholds as function of stimulation rate. Data from stimulation of 3 different electrodes are shown. Filled circles indicate group mean thresholds for single pulses. Open circles indicate group mean thresholds for 400-Hz pulse train. Filled squares indicate group mean thresholds for 1,000-Hz pulse train. Error bars indicate ±1 standard deviation from mean.

One of the striking findings of this study is the extent of intrasubject variability that exists in these data. For some subjects, EABR thresholds obtained with a slow-rate stimulus appropriate for electrophysiological testing are recorded at levels that are considerably lower than the level of the programming stimulus they judged to be most comfortable. For other subjects, EABR thresholds indicate a stimulation level that would exceed the level judged to be uncomfortable for the programming stimulus. We have suggested previously that differences in temporal integration across subjects may account for some of this variability. Consequently, we attempted to measure temporal integration directly by measuring psychophysical thresholds for a single pulse and for 2 different frequency pulse trains. Figure 5 shows average thresholds for single pulses (filled circles)

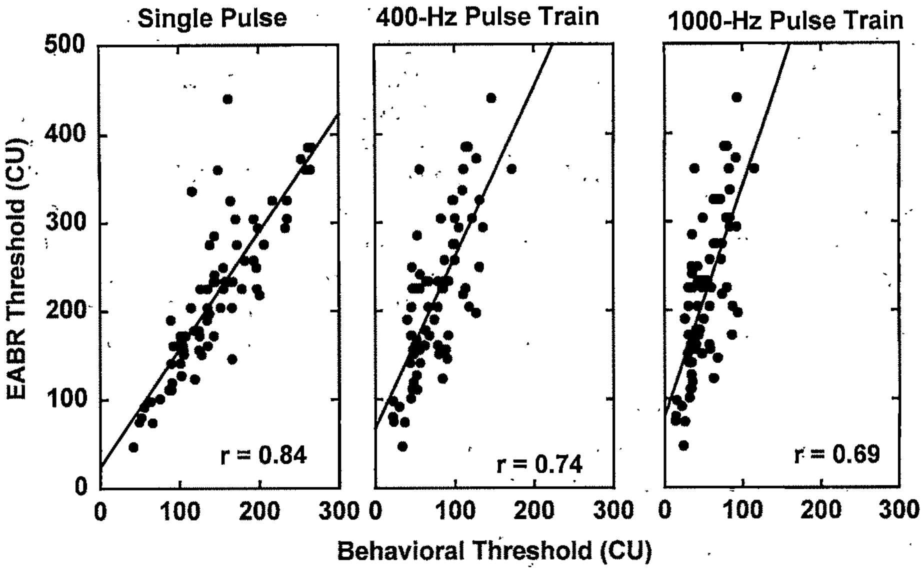


Fig 6. Relationship between EABR threshold recorded with 13.1-Hz biphasic pulse train and psychophysical thresholds for 3 different stimuli. In left panel, stimulus used to obtain psychophysical threshold was single biphasic current pulse. In middle panel, psychophysical thresholds were measured with 400-Hz pulse train. In right panel, psychophysical thresholds were measured with 1,000-Hz pulse train. Solid line indicates linear regression of data.

and for a 400- and 1,000-Hz pulse train (open circles and filled squares, respectively). Clearly, increasing stimulus frequency leads to a reduction in behavioral threshold. This pattern was true for all subjects. However, the magnitude of the change in threshold (temporal integration) varied from person to person.

The left panel of Fig 6 shows the correlations obtained between EABR thresholds and thresholds for a single pulse. There is a strong correlation between these 2 measures. The correlation is weaker between EABR threshold and behavioral threshold for a 400-Hz or a 1,000-Hz pulse train. If cochlear implant subjects are not able to perform temporal integration or if they all have similar temporal integration abilities, all 3 correlation coefficients should be similar. Changes in correlation coefficients also may be due to the fact that the range across which the psychophysical threshold varies becomes relatively more restricted as the stimulus frequency is increased.

In Fig 7, the difference between EABR threshold and the threshold for the pulse train used to program the Clarion speech processor is plotted as a function of the difference between psychophysical thresholds for a single pulse and for a pulse train. In both panels, the variable plotted on the abscissa should be an index of temporal integration. Subjects who are able to perform efficient temporal integration have relatively large differences between their behavioral threshold for a single pulse and their threshold for a pulse train. Subjects who show less temporal integration have relatively small differences between their threshold for a single pulse and their behavioral

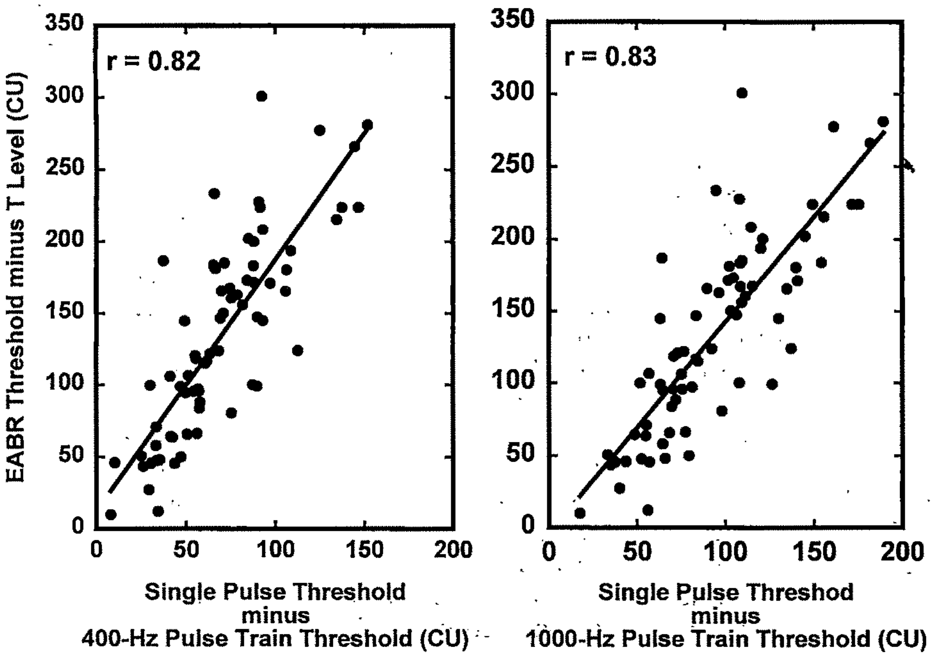


Fig 7. Difference between EABR threshold and T level is plotted as function of difference between single pulse threshold and threshold for 400- or 1,000-Hz pulse train. Panel on left shows data obtained with 400-Hz pulse train. Panel on right shows data obtained with 1,000-Hz pulse train. Solid line indicates linear regression of data. Correlation coefficients are shown in top left-hand corner of each panel.

threshold for a pulse train. In both panels, the variable plotted on the ordinate shows how close EABR threshold comes to predicting threshold for the programming stimulus. The panel on the left shows results obtained with a 400-Hz pulse train for psychophysical detection thresholds. The panel on the right shows results obtained with a 1,000-Hz stimulus. We interpret the significant correlation coefficients to suggest that the variability in the data shown in Fig 3 can be attributed, in large part, to differences in temporal integration across subjects.

DISCUSSION

The purpose of this study was to examine how EABR thresholds recorded from patients who use the Clarion cochlear implant correlate to the levels used to program the speech processor. The data we have shown suggest that EABR thresholds for Clarion cochlear implant users are obtained at levels that approximate behavioral "most comfortable levels," or M levels, rather than behavioral threshold levels. However, the extent of the intrasubject variability is substantial. For some subjects, EABR threshold is recorded at current levels that would be near the bottom of the subject's dynamic range. For other subjects, EABR threshold is obtained at current levels that may slightly exceed UCL for the pulse train stimulus used to program the processor. This variability means that for a large percentage of subjects, setting their processor on the basis of EABR thresholds exclusively would lead to significant errors.

A conservative clinical approach might be to view a level just under EABR threshold as a level at which one knows the subject can hear the pulse train stimulus but at which stimulation typically will not be uncomfortable. This level can be a useful point to begin conditioning a young, congenitally deaf child to respond to initial electrical stimulation, thus facilitating, rather than replacing, traditional behavioral programming of the device. In situations in which the subject is unable to respond behaviorally to electrical stimulation, a level just below EABR threshold may be a good point to set the maximum stimulation levels rather than device thresholds.

The Clarion data reported here are not dissimilar to results we have published previously for persons using the Nucleus cochlear implant. In that study, we found that on average, EABR thresholds were recorded approximately two thirds of the way between the behavioral thresholds (T levels) and the maximum comfort levels (C levels) used to program the Nucleus device. However, significant intrasubject variability was observed.[6] The EABR thresholds did not correlate strongly with either behavioral T or C levels, but were recorded at stimulation levels for which the 250-Hz pulse train used to program the speech processor was always audible and was virtually never above the level judged by the subject to be his or her maximum comfortable stimulation level. We felt the intrasubject variability was too large to allow us to recommend basing the speech processor threshold or maximum comfort levels directly on the electrophysiological results. We did, however, suggest ways in which EABR thresholds could be used to facilitate the process of fitting the speech processor to the individual user.

It is difficult to compare the results of the 2 studies directly, because of the differences in stimulus variables used to program the Clarion and Nucleus speech processors. Specifically, for subjects using the Clarion cochlear implant, EABR thresholds recorded with a slow-rate stimulus appropriate for electrophysiological testing correspond to a level somewhat higher in the subjects' dynamic range for the pulse train used to program the speech processor than is observed with Nucleus cochlear implant users. However, in the Nucleus study, the upper limit for the behavioral dynamic range for each electrode was a level described by the subjects as the "maximum comfortable level," and in that study, we did not measure the subjects' UCLs. In the Clarion study, the parameter used to program the speech processor was the subject's "most comfortable level," a level considerably lower than the subject's uncomfortable level.

The pulse rate used in programming also is different for the Clarion and Nucleus speech processors. One may expect EABR thresholds to be somewhat more variable and to be recorded at levels somewhat higher in the subject's dynamic range for Clarion users than for Nucleus users, because the Nucleus programming stimulus is a 250-Hz pulse train, while the Clarion programming stimulus ranges between 434 and 916 Hz for most patients. As illustrated in Fig 5, behavioral thresholds, and presumably also MCLs and UCLs, decrease as the stimulus rate increases, because behavioral levels are influenced by the subject's ability to perform temporal integration. Consequently, EABR thresholds for Clarion users should be obtained at current levels that are higher in the dynamic range than those of Nucleus implant users, because the behavioral dynamic range measures for the Clarion device are obtained with a higher stimulation rate. Notably, Cochlear Corporation recently has introduced a cochlear implant system that allows for faster stimulation rates. Programming high-rate processors will be accomplished with correspondingly higher-frequency pulse trains. As stimulation rates are increased, the correlation between EABR thresholds and behavioral programming variables will need to be readdressed.

One factor that is similar between the results obtained with Nucleus patients and Clarion users is that there is considerable intrasubject variability for both groups. Regardless of implant type, for some subjects, EABR thresholds are obtained at current levels that are relatively low in the subject's dynamic range for a pulse train. For other subjects, EABR thresholds are recorded at levels closer to the UCL. We have hypothesized previously that this variability may be due in part to individual differences in temporal integration ability.

We have attempted to address this issue directly here, and 2 findings support our hypothesis. First, we have shown that EABR thresholds correlate more strongly with behavioral thresholds for a single pulse than they do for a 1,000-Hz pulse train (Fig 6). Second, as we have shown in Fig 7, subjects with good temporal integration (ie, those that have large differences between their thresholds for a single pulse and their thresholds for a pulse train) tend to be subjects for whom there is a large difference between their electrophysiological and behavioral programming thresholds. For subjects with very limited temporal integration abilities, EABR thresholds are recorded at relatively lower levels in their dynamic range for the programming stimulus. It may be that we could improve the correlation between EABR thresholds and behavioral programming thresholds if we could estimate the subject's temporal integration abilities for a specific electrode.

ACKNOWLEDGMENTS — The authors thank Jonathan Gervais and Abigail Wolaver for assistance with data collection and analysis.

REFERENCES

1. Fryauf-Bertschy H, Tyler RS, Kelsay DM, Gantz BJ, Woodworth GP. Cochlear implant use by prelingually deafened children: the influences of age of implant and length of device use. J Speech Hear Res 1997;40:183-99.

2. Miyamoto RT, Svirsky MA, Robbins AM. Enhancement of expressive language in prelingually deaf children with cochlear implants. Acta Otolaryngol (Stockh) 1997;117:154-7.

3. Tyler RT, Fryauf-Bertschy H, Kelsay DMR, Gantz BJ, Woodworth GP, Parkinson A. Speech perception by prelingually deaf children using cochlear implants. Otolaryngol Head Neck Surg 1997;117:180-7.

4. Osberger MJ. Cochlear implantation in children under the age of two years: candidacy consideration. Otolaryngol Head Neck Surg 1997;117:145-9.

5. Hall JW. Handbook of auditory evoked responses. Boston, Mass: Allyn and Bacon, 1990.

6. Brown CJ, Abbas PJ, Frayauf-Bertschy H, Kelsay D, Gantz BJ. Intraoperative and postoperative electrically evoked auditory brain stem responses in Nucleus cochlear implant users: implications for the fitting process. Ear Hear 1994;15:168-76.

7. Shallop JK, Beiter AL, Goin DW, Mischke RE. Electrically evoked auditory brain stem responses (EABR) and middle latency responses (EMLR) obtained from patients with the Nucleus multichannel cochlear implant. Ear Hear 1990;11:5-15.

8. Shallop JK, VanDyke L, Goin DW, Mischke RE. Prediction of behavioral threshold and comfort values for Nucleus 22-channel implant patients from electrical auditory brain stem response test results. Ann Otol Rhinol Laryngol 1991;100:896-8.

9. Kileny PR. Use of electrophysiologic measures in the management of children with cochlear implants: brainstem, middle latency, and cognitive (P300) responses. Am J Otol 1991;12 (suppl 12):37-42.

10. Mason SM, Sheppard S, Garnham CW, Lutman ME, O'Donoghue GM, Gibbin KP. Improving the relationship of intraoperative EABR thresholds to T-level in young children receiving the Nucleus cochlear implant. In: Advances in cochlear implants. Proceedings of the 3rd International Cochlear Implant Conference, Innsbruck, Austria, 1994:44-9.

11. Abbas PJ, Brown CJ. Electrically evoked auditory brain stem response: growth of response with current level. Hear Res 1991;51:123-37.

Ann Otol Rhinol Laryngol 108:1999

ELECTRICALLY EVOKED POTENTIALS RECORDED IN ADULT AND PEDIATRIC CLARION® IMPLANT USERS

JILL B. FIRSZT, PHD
URBANA, ILLINOIS
LEE ANN ROTZ, MA
URBANA, ILLINOIS
RON D. CHAMBERS, PHD
CHAMPAIGN, ILLINOIS
MICHAEL A. NOVAK, MD
URBANA, ILLINOIS

The purpose of this study was to record electrical auditory brain stem responses (EABRs) and electrical middle latency responses (EMLRs) in the clinic from 3 adult CLARION® Multi-Strategy™ Cochlear Implant subjects and to record EABRs in the operating room from 3 pediatric subjects. For 2 of the 3 adult subjects, EABR thresholds were within the subject's behavioral dynamic range, whereas 1 adult subject's EABR thresholds were either absent or, when present, exceeded the upper limit of the dynamic range. For this subject, EMLRs were absent or of poor morphology for the channels tested. Moreover, this subject was not able to understand speech in an open-set, auditory-only format. The EABR thresholds obtained with children were within the behavioral dynamic range for 2 of the 3 subjects, but exceeded comfortable loudness levels for 1 subject. Although the EABR thresholds were measured at stimulus levels that were audible for all subjects, the relationship of the EABR threshold levels to behavioral measures of loudness varied. Evoked potentials that originate more centrally, such as the EMLR, should be investigated further to determine the possible relationship to postimplant performance.

KEY WORDS — cochlear implant, electrical stimulation, electrically evoked auditory brainstem response, electrically evoked middle latency response, electrophysiological measures.

INTRODUCTION

Electrically evoked potentials have been studied in cochlear implant users for several purposes, including assessment of neural integrity, implant function, and spiral ganglion cell survival.[1-4] The use of middle and late latency electrically evoked potentials has been pursued in an attempt to better understand the variability observed in patient performance.[5-8] As the age at implantation has decreased, programming the external implant equipment has become more challenging.[9] Objective tools, such as the electrically evoked auditory brain stem response, may assist in determining appropriate threshold and comfortable loudness levels,[10] especially for children who have little auditory experience and limited language.[11,12] While there are a number of published studies that have reported electrically evoked potential findings,[1-8,10-14] there are no reports of electrically evoked potentials in subjects who have received the CLARION® Multi-Strategy™ Cochlear Implant. This paper describes a technique to record the electrical auditory brain stem response (EABR) and the electrical middle latency response (EMLR) from a pilot group of adult and pediatric Clarion cochlear implant recipients. These preliminary findings explore the characteristics of electrically evoked potentials in Clarion users, their relationship to programming levels, and their possible relationship to postimplant performance.

METHODS

The subjects were 3 adults (2 women and 1 man) and 3 children (2 girls and 1 boy) who had received the Clarion implant. All subjects had complete electrode array insertions. At the time of testing, the adult subjects were 29, 32, and 54 years of age, while the pediatric subjects were 2 years; 2 years 5 months; and 3 years 4 months of age. Additional background information for all subjects is provided in the Table, along with speech perception scores for adult subjects. Due to the short length of implant use for the pediatric subjects, speech perception skills were not evaluated.

Figure 1 is a schematic that illustrates the equipment used to record electrically evoked potentials. Stimuli were presented through an Ascentia 910 laptop computer connected to a clinician's programming interface (CPI) unit, a speech processor (SP), and the subject's headpiece (HP). A radio frequency (RF) filter was positioned between the recording electrodes and the amplifier to reduce stimulus artifact. Stimuli were 75-microsecond (μs) biphasic current pulses delivered to the internal electrodes with medial monopolar stimulation. Electrically evoked poten-

---

From the Department of Otolaryngology–Echo Program, Carle Clinic Association, Urbana (Firszt, Rotz, Novak), and the Department of Speech and Hearing Science, University of Illinois, Champaign (Firszt, Chambers), Illinois.

Portions of this paper were presented at the meeting of the American Academy of Audiology, Ft Lauderdale, Florida, April 17-20, 1997.

CORRESPONDENCE — Jill B. Firszt, PhD, Carle Clinic Association, 602 W University Ave, Urbana, IL 61801.

BACKGROUND INFORMATION FOR THREE ADULT AND THREE PEDIATRIC CLARION IMPLANT USERS

		Profound Hearing Loss					
Subject	*Age at Test*	*Cause*	*Age at Onset*	*Length of Auditory Deprivation*	*Length of Implant Use*	*CID Sentence*	*NU6 Word*
1	54 y	Progressive	50 y	3 y	18 mo	100%	72%
2	29 y	Familial progressive	9 y	16 y	4 y	0%	0%
3	32 y	Autoimmume sudden	31 y	1 y 6 mo	5 mo	98%	72%
4	2 y 5 mo	Meningitis	8 mo	1 y 9 mo	2 mo	NA	NA
5	2 y	Familial progressive	Birth	2 y	2 mo	NA	NA
6	3 y 4 mo	Familial progressive	Birth	3 y 4 mo	2 mo	NA	NA

CID Sentence — percent correct on 2 CID Sentence lists presented auditory-only; NU6 Word — percent correct on 1 NU6 word list presented auditory-only; NA — not applicable.

tial responses were recorded with a Nicolet Compact 4 (C4) electrodiagnostic system externally triggered by the stimulus output of the SCLIN for Windows software and the interface unit. For the evoked potential testing, stimulus rates of 20.03 Hz (EABR) and 9.3 Hz (EMLR) were used. Behavioral measures of threshold (T), most comfortable loudness level (M), and upper limit of comfort level (ULCL) were obtained with the slow rates to compare to the electrically evoked potentials. In addition, behavioral measures were obtained with a stimulus rate of 833 Hz, (the rate used to program the speech processor) and also were compared with the electrically evoked potentials.

The EABR was recorded with either gold cup surface electrodes or subdermal needle electrodes placed on the forehead, on the nape of the neck, and on the earlobe either contralateral to the implant (clinic recordings) or ipsilateral to the implant (operating room recordings). For the EABR, each recording was replicated twice, with 1,000 sweeps for the clinic recordings, and 500 for those in the operating room. The recording window was 10 milliseconds (ms), and responses were filtered between 100 and 3,000 Hz. For the EMLR, the same electrode montage was used to obtain 2 replications of 500 sweeps for each response, with a 50-ms recording window and a response bandwidth between 5 and 500 Hz.

The EABRs and EMLRs were recorded by stimulating channels 1, 4, and 7, which represent electrical stimulation at apical, middle, and basal locations within the cochlea. Stimulus levels used in the clinic were within the behavioral dynamic range for each subject on each channel, and were decreased until the evoked potential threshold was obtained. Stimulus levels in the operating room included levels used during pilot recordings that typically yielded a well-formed response, and again were decreased as threshold was determined. The electrically evoked potential threshold (EABR, EMLR) was defined as the lowest stimulus level at which a repeatable response could be visually detected.

For adult subjects in the clinic, EABR testing was conducted with subjects relaxed or asleep in a reclining chair. The subjects were asked to remain awake and alert during the EMLR testing. For recordings for children in the operating room, EABR results were obtained following insertion of the internal device and while the subjects were under general anesthesia.

For behavioral measures obtained with adult subjects, threshold (T) was defined as the average level at which the subject responded on 4 ascending trials. The most comfortable loudness level (M) was defined as the level perceived to be comfortably loud on 3 consecutive trials, while the upper limit of com-

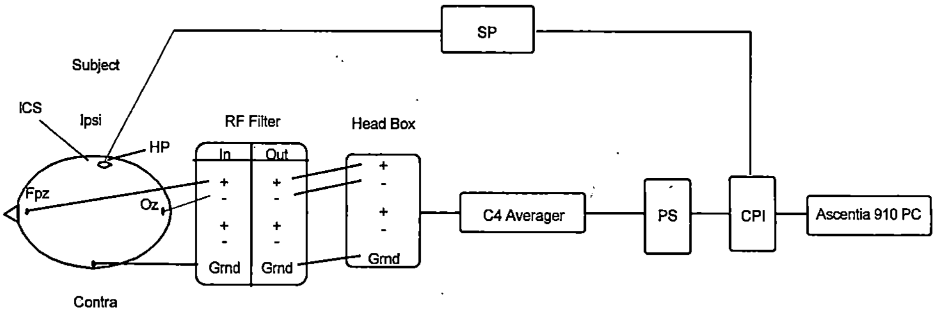


Fig 1. Equipment connections for electrical evoked potential testing. HP — headpiece, ICS — implantable cochlear stimulator, SP — speech processor, PS — pulse stretcher, CPI — clinician programming interface unit, RF — radio frequency, Grnd — ground.

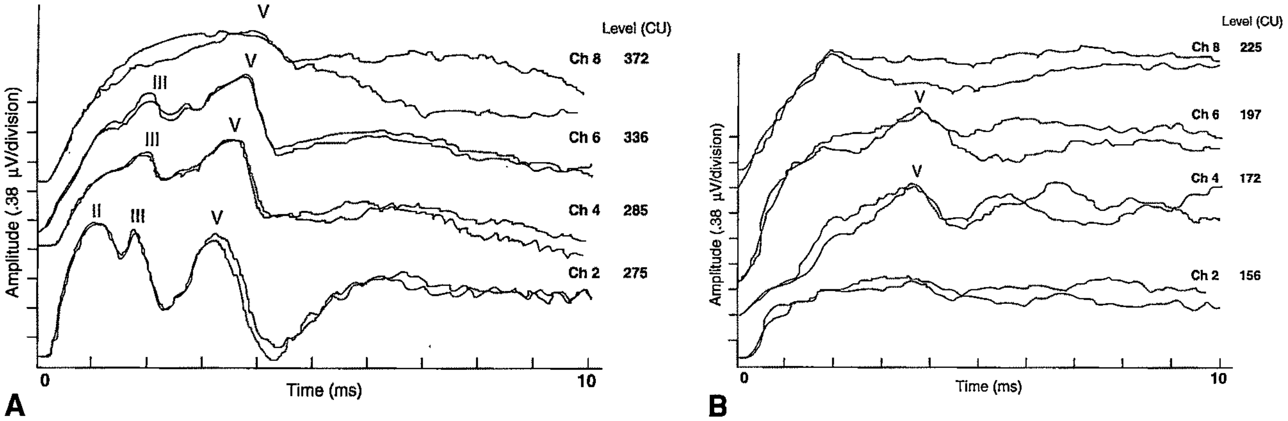


Fig 2. Electrical auditory brain stem response (EABR) waveforms obtained postimplantation in the clinic from 2 adult subjects at most comfortable loudness (M) level. Recordings from channels (Ch) that represent apical (channel 2) to basal (channel 8) stimulation are displayed for subject 3 (A) and subject 2 (B). Identifiable waves and response morphology differ across channels and subjects. Stimulus artifact was removed off-line to improve comparison between waveforms. CU — clinical units.

fort level (ULCL) was the level perceived to be the maximum loudness level that could be tolerated for several minutes on 3 consecutive trials. For children, T was the lowest level at which a conditioned or an observable behavioral response was given; M was the maximum level that appeared comfortably loud, but not too loud. The ULCLs were not determined for the pediatric subjects. It is possible that the M levels for pediatric subjects were similar to a level between M and ULCL for adult subjects.

RESULTS

Clinic recordings from various stimulation sites along the electrode array are compared for adult subjects 1 and 2 in Fig 2. All recordings in Fig 2 were obtained at the subject's M level. Figure 2A shows recordings for subject 1 for channels 2, 4, 6, and 8. Wave V was present on all channels for this subject. The latency of wave V increased (approximately 0.70 ms) as recordings were obtained from channel 2 (apical) to channel 8 (basal), and were slightly earlier than those typically noted for the acoustic auditory brain stem response (ABR). For this subject, waveform morphology was judged to be better for recordings on the more apical channels, where waves II and/or III, as well as V, are evident. Wave I is not observable on any recordings. Only wave V was observed for the most basal channel. The amplitude of wave V is largest for channel 2 (1.47 µV) and smallest for channel 8 (0.24 µV). The recordings in Fig 2B for subject 2 reveal that wave V is absent for channels 2 and 8. In addition, the earlier waves II and III are absent on all channels, and waveform morphology was judged to be poor overall.

The repeatability across sessions of wave V latency (microseconds) and amplitude (microvolts) was evaluated over a 1-year period for each of these adult subjects. The EABR recordings for channels 1, 4, and 7 were obtained at the subject's M level on 2 or 3 occasions during the 1-year period. For this purpose, the behavioral M level was determined with a stimulus rate of 20.03 Hz (the same rate as that used to record the EABR). The waveforms showed good replication across sessions. When present on a channel, wave V latency was within 0.20 ms from one test session to another. Wave V amplitude for the 3 subjects varied from 0.07 to 0.42 µV across test sessions.

Figure 3 shows EABR thresholds compared to behavioral T, M, and ULCL for the slow rate (20.03 Hz) used to record the EABR and the fast rate (833 Hz) used to determine the subject's program for daily listening. Generally, T, M, and ULCL measures are lower at the fast rate than at the slower rate. For all subjects, the EABR threshold tended to be higher for channel 7 than for channels 1 and 4. The EABR thresholds were obtained for all subjects across electrodes at electrical current levels of 140 to 340 Clinical Units (CU). For subjects 1 and 3, the EABR threshold falls essentially between T and M levels for both the slow and fast rates on all 3 channels. For subject 2, when comparing the slow rate stimuli (in Fig 3A), the EABR threshold falls closer to M level for channels 1 and 4, and near ULCL for channel 7. When comparing EABR threshold to the fast rate behavioral measures for subject 2 (Fig 3B), the threshold falls above the ULCL for all channels. Subject 2 also has a reduced dynamic range compared to the other subjects, regardless of the stimulus rate.

In Fig 4, EMLR recordings are displayed for the 3 adult subjects for channel 1 at each subject's M level. The negative polarity peak, Na, and the positive polarity peak, Pa, were obtained from 2 of the 3

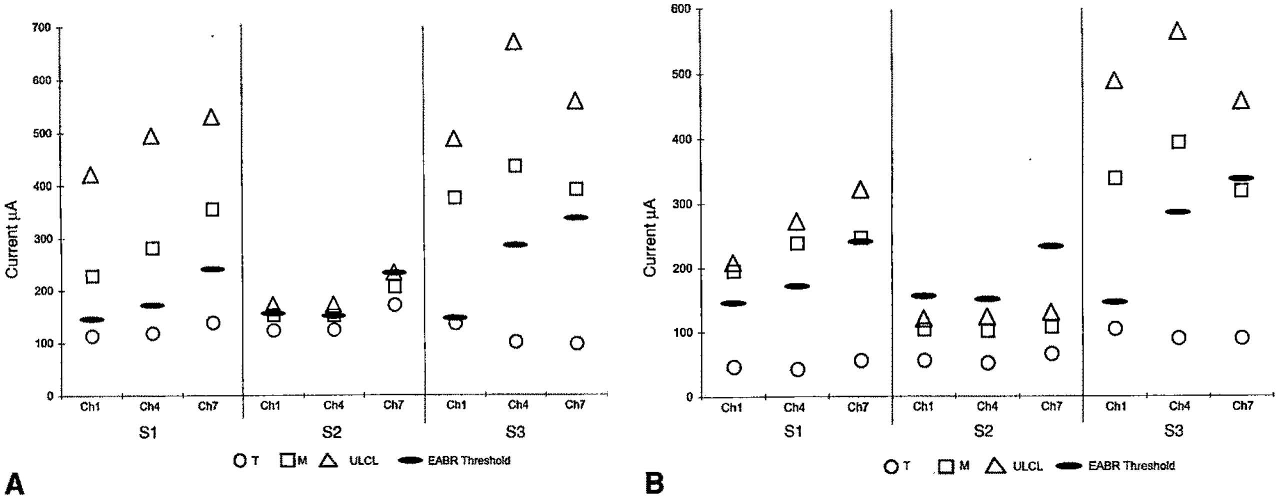


Fig 3. Threshold (T), M level, and upper limit of comfort level (ULCL) obtained at 2 stimulus rates and EABR thresholds are plotted for subjects 1 to 3 (S1 to S3). A) Results with stimulus rate of 20.03 Hz (used to obtain EABR). Scale extends to 700 µA. B) Results with stimulus rate of 833 Hz (used to program speech processor). Scale extends to 600 µA.

subjects (subjects 1 and 3). The waveforms show good replication and appear similar in latency and morphology to the conventional acoustic MLR. For subjects 1 and 3, Na latencies were 17 to 18 ms and Pa latencies were 26 to 30 ms. The amplitudes for the Na-Pa complex were 1.0 to 2.7 µV. Subjects 1 and 3 showed replicable EMLRs on the other channels tested (4 and 7) as well. For subjects 1 and 3, EMLR thresholds were within each subject's behavioral dynamic range. Responses were absent for subject 2 at M level and for higher current levels. In addition, EMLRs were absent or of poor morphology for the other 2 channels.

The EABR recordings were obtained in the operating room at the time of surgery for the 3 pediatric subjects (subjects 4, 5, and 6). Figure 5 shows recordings made for subject 4 as current level was decreased on channel 1. Waves III, IV, and V are present across current levels from 411 to 161 CU. Wave V is observable at a current level of 141 CU and was judged to be threshold. The latency of wave V increased from 4.10 to 4.58 ms, and the amplitude decreased from 1.64 to 0.39 µV.

In Fig 6, EABR thresholds obtained in the operating room for channels 1, 4, and 7 were compared to each pediatric subject's T and M levels obtained during device programming 2 months after surgery. For 2 of the 3 subjects, EABR thresholds on channel 7 were above (subject 5) or substantially higher (subject 6) than the M level. For subject 4, the EABR thresholds were near the behavioral threshold for all channels. The EABR thresholds were between T and M levels for subject 5 on channels 1 and 4. For subject 6, EABR thresholds were either between T and M (channel 1), or above M (channel 4). It should be noted that subject 6 was not able to tolerate these M

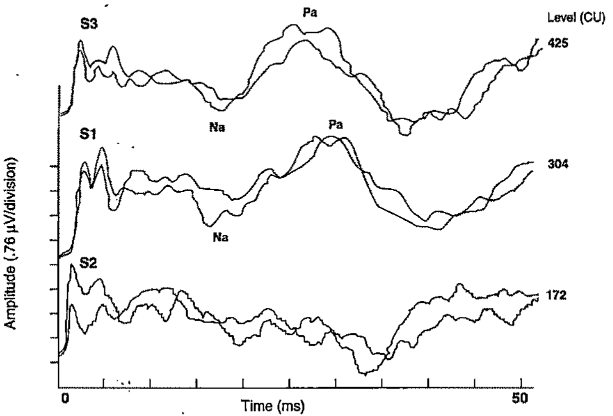


Fig 4. Electrical middle latency response (EMLR) recordings on channel 1 for subjects 1 to 3 (S1 to S3) at each subject's M level. Waves Na (negative polarity peak) and Pa (positive polarity peak) are present and repeatable for subjects 1 and 3, but absent for subject 2.

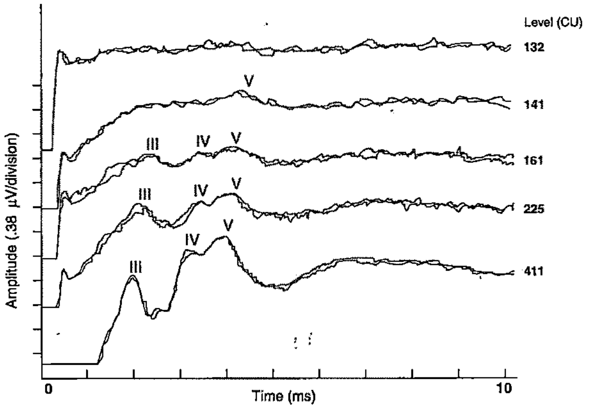


Fig 5. EABR traces recorded in operating room from pediatric subject (subject 4) on channel 1. Two recordings are shown for each current level ranging between 411 and 132 µA. Waves III, IV, and V are identifiable at higher current levels, and wave V is followed to threshold (141 µA).

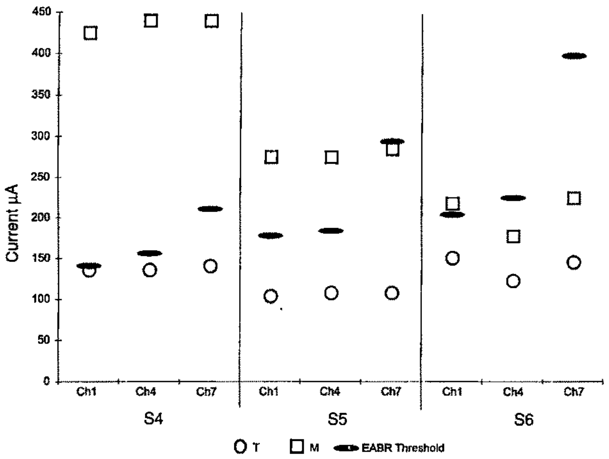


Fig 6. Behavioral T and M levels obtained during programming at 2 months postimplantation for pediatric subjects 4 to 6 (S4 to S6), compared to EABR thresholds recorded at time of surgery. Stimulus rate was 833 Hz. Relationship between EABR threshold and dynamic range varies across subjects and channels.

levels when all channels were later activated during response to speech stimuli. It was necessary to lower the M levels below those displayed in Fig 6 so that listening to speech in all environments would be comfortable.

DISCUSSION

Electrically evoked potentials were recorded reliably from adult and pediatric Clarion cochlear implant users. Recordings for adults were obtained in the clinic, and those for children in the operating room. With electrical stimulation, variation was observed across subjects and across channels within subjects.

For adults, the recordings were consistent over time in individuals. The morphology of the electrically evoked waveforms appeared to be similar to those generated by an acoustic signal. The EABR wave I was not observable in any recordings, due to stimulus artifact. The EABR waves II, III, IV, and V had latencies that appeared slightly earlier and amplitudes that were slightly larger than is typical of acoustically elicited waveforms. This difference is likely a result of the absence of cochlear transmission and the direct neural firing that occurs with electrical stimulation.[3,13] The EMLRs were recorded reliably in the clinic from 2 of 3 adult implant users. For these subjects, the Na and Pa latencies and morphology were similar to those expected with an acoustic stimulus. For the other adult subject, the evoked responses were either poorly formed or not present. For this subject, EABRs were absent on 3 of 8 tested channels, and EMLRs were either absent or of poor reliability on all tested channels.

For adults, T, M, and ULCL were determined with 2 stimulus rates: 20.03 Hz and 833 Hz. Behavioral T, M, and ULCL levels were lower with the faster rate than with the slower rate, possibly due to temporal integration.[3,11] The EABR thresholds fell within the dynamic range obtained with both rates for 2 of the adult subjects. For the other adult subject, the EABR thresholds fell above the ULCL obtained with the fast rate, and within the range for 2 of 3 electrodes with the slower rate. This pattern suggests that the EABR threshold could have been used to estimate programming thresholds for 2 of the 3 adults. For adult subject 2, the EABR threshold exceeded the behavioral ULCL when obtained at the fast rate. This subject also had an extremely reduced dynamic range, and lower M and ULCL behavioral measures, making it more likely that the EABR threshold might exceed the M level or ULCL.

For the pediatric subjects, the EABR thresholds on channel 1 were within the behavioral dynamic range. For channel 4, the EABR threshold was above the M level for 1 subject. For channel 7, it was above the M level for 2 subjects. These results suggest that the current levels used to elicit EABR thresholds in the operating room will be current levels that are audible during later device programming. The perceptual loudness of this level will vary from one child to another, but will most likely not fall below behavioral threshold. Results from subject 6 suggest that caution should be exercised when using EABR thresholds to estimate programming levels, especially for basal channels, because the EABR threshold level may exceed a behavioral M level. Since the behavioral T and M levels were collected at 2 months postimplantation for the pediatric subjects, it is anticipated that the T and M levels may change over time (due to more experience with the implant and with the programming task). The relationship between the EABR threshold and behavioral levels may vary with time, and also should be evaluated at later intervals. Nonetheless, a relationship between the EABR thresholds obtained at the time of surgery and early programming levels may be particularly valuable for determining acceptable initial current levels that are audible and comfortable for young children.

Adult subjects 1 and 3 (with well-formed EABRs and EMLRs) demonstrate substantial open-set word understanding in the auditory-only condition (see Table). Although subject 2 reports benefit from the implant, she is not able to understand words or sentences in an open-set format. This subject also demonstrates poor or absent electrically evoked potential responses (EABR, EMLR) for the channels tested in this study.

CONCLUSIONS

The results suggest that EABR thresholds may be elicited by stimulus levels that are audible for adults and children. This correspondence may be useful with young children, who are not able to give reliable behavioral information. However, since the current level that elicits EABR threshold may exceed a comfortable listening level for some subjects, especially on the basal channels, it should be used in a conservative manner. The relationship between EABR threshold and behavioral perception of loudness should be studied longitudinally, particularly in children. Furthermore, it has been suggested that evoked potentials such as EABR and EMLR might relate to a subject's postimplant performance, although initial results have not provided strong evidence.[14] In this study, the 2 adults who showed good auditory performance with the implant also had well-formed evoked potentials, while the adult with poor performance had poor or absent electrical responses. These relationships are being investigated further in a larger sample of subjects.

ACKNOWLEDGMENTS — This pilot work was conducted as part of a doctoral dissertation at the University of Illinois by the first author. We thank the Carle Foundation, Carle Clinic, University of Illinois, and Advanced Bionics Corporation for financial support. We also thank Ruth Reeder and Mike Thomas for technical assistance.

REFERENCES

1. Abbas PJ, Brown CJ. Electrically evoked brain stem potentials in cochlear implant patients with multi-electrode stimulation. Hear Res 1988;36:153-62.

2. Jyung RW, Miller JM, Cannon SC. Evaluation of eighth nerve integrity by the electrically evoked middle latency response. Otolaryngol Head Neck Surg 1989;101:670-82.

3. van den Honert C, Stypulkowski PH. Characterization of the electrically evoked auditory brain stem response (ABR) in cats and humans. Hear Res 1986;21:109-26.

4. Mahoney MJ, Rotz-Proctor LA. The use of averaged electrode voltages to assess the function of Nucleus internal cochlear implant devices in children. Ear Hear 1994;15:177-83.

5. Kileny PR, Kemink JL. Electrically evoked middle latency potentials in cochlear implant candidates. Arch Otolaryngol Head Neck Surg 1987;113:1072-7.

6. Kraus N, Micco AG, Koch DB, et al. The mismatch negativity cortical evoked potential elicited by speech in cochlear implant users. Hear Res 1993;65:118-24.

7. Micco AG, Kraus N, Koch DB, et al. Speech-evoked cognitive P300 potentials in cochlear implant recipients. Am J Otol 1995;16:514-20.

8. Ponton CW, Don M. The mismatch negativity in cochlear implant users. Ear Hear 1995;16:130-46.

9. Firszt JB, Reeder RM. Cochlear implants and children: device programming and considerations for young children. Semin Hear 1996;17:337-52.

10. Shallop JK, VanDyke L, Goin DW, Mischke RE. Prediction of behavioral threshold and comfort values for Nucleus 22-channel implant patients from electrical auditory brain stem response test results. Ann Otol Rhinol Laryngol 1991;100:896-8.

11. Brown CJ, Abbas PJ, Fryauf-Bertschy H, Kelsay D, Gantz BJ. Intraoperative and postoperative electrically evoked auditory brainstem response in Nucleus cochlear implant users: implications for the fitting process. Ear Hear 1994;15:168-76.

12. Mason SM, Sheppard S, Garnham CW, Lutman ME, O'Donoghue GM, Gibbin KP. Improving the relationship of intraoperative EABR thresholds to T-level in young children receiving the Nucleus cochlear implant. In: Hochmair-Desoyer IJ, Hochmair ES, eds. Advances in cochlear implants. Vienna, Austria: Manz, 1994:44-9.

13. Abbas PJ. Electrophysiology. In: Tyler RS, ed. Cochlear implants: audiological foundations. San Diego, Calif: Singular Publishing Group, 1993:317-56.

14. Brown CJ, Abbas PJ, Bertschy M, et al. Longitudinal assessment of physiological and psychophysical measures in cochlear implant users. Ear Hear 1995;16:439-49.

Ann Otol Rhinol Laryngol 108:1999

USING ELECTRICALLY EVOKED AUDITORY REFLEX THRESHOLDS TO FIT THE CLARION® COCHLEAR IMPLANT

ANNELLE V. HODGES, PHD
STACY BUTTS, MA
SHELLY DOLAN-ASH, MS
THOMAS J. BALKANY, MD

MIAMI, FLORIDA

This paper describes a method for measuring electrically elicited auditory reflex thresholds (EARTs) in young children who use the CLARION® Multi-Strategy™ Cochlear Implant. The EART is an objective measure that can guide the fitting of a cochlear implant in individuals who are unable to perform behavioral tasks required to program the device. Reflexes were obtained in 11 of 17 pediatric Clarion users. The EART current level indicated a point at which an auditory percept was present and the sound was loud, but not uncomfortable. The EART then was used as a basis for conditioning behavioral responses, and as a guideline for setting most comfortable loudness levels.

KEY WORDS — acoustic reflex, cochlear implant.

INTRODUCTION

Researchers and clinicians have been interested in the development of objective measures for the programming of cochlear implants since these devices first became clinically useful. Both evoked potentials and stapedial reflexes have attracted attention as potential methods of obtaining objective programming data.[1-7] As early as 1986, Jerger et al[8,9] concluded that measurement of electrically elicited auditory reflex thresholds (EARTs) provided useful data for programming the external components of cochlear implants.

As the minimum age of implantation has continued to decrease, the need for objective ways to program speech processors has become more important. In the population under 2 years of age, the lack of auditory experience, together with the limited language abilities especially evident in deaf children, makes the task of setting threshold and upper comfort levels a long-term, ongoing process. Pediatric audiologists with sufficient experience in working with both cochlear implants and very young children are often quite accurate in their ability to judge levels on the basis of the child's behavior.

However, there are some occasions and some children for whom determining accurate programming levels challenges even the best of clinicians. In addition, as more centers begin to implant very young children, the audiologists programming these children may not have the level of experience and expertise of clinicians in older, more established centers. Often, implanted children must return to the clinic many times, each time providing more behavioral auditory information. Thus, children may go for several months using a different program each week. Therefore, both for clinicians experienced with very young children and for less experienced clinicians just beginning to work with children, objective measures for obtaining programming data could reduce the uncertainty in programming and allow clinicians to develop better programs in a more timely fashion with fewer program changes. Clearly, there would be significant benefit to achieving an accurate and stable program in as short a period as possible.

Setting levels of minimal stimulation, or threshold, in children generally is accomplished successfully with traditional pediatric audiology techniques such as conditioned play audiometry, visual reinforcement audiometry, or tangible reinforcement operant conditioning audiometry. The procedures are similar to those used in obtaining an audiogram, requiring a child to pair a stimulus with a response. Children who are candidates for cochlear implantation usually are familiar with the stimulus-response paradigm. Nonetheless, they still must be sound-conditioned prior to implantation. Alternatively, visual or tactile stimuli can be used to teach the child the task. Learning to pair a response with a stimulus can be accomplished even by a very language-limited child.

In contrast, setting levels for the upper comfort level requires that the individual make a judgment about the sound beyond simple presence or absence. Few children under the age of 2 — even with nor-

---

From the University of Miami Ear Institute, Miami, Florida.

CORRESPONDENCE — Annelle V. Hodges, PhD, Dept of Otolaryngology HNS (D-48), University of Miami School of Medicine, PO Box 016960, Miami, FL 33101.

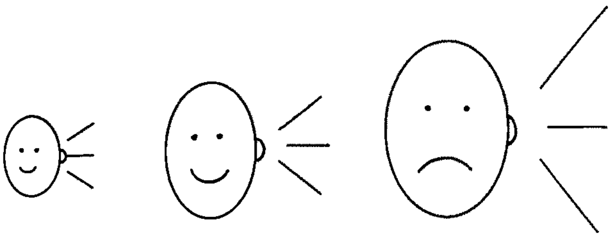


Fig 1. Sample pictures used in programming children. Each face indicates sounds that are soft, good, or too loud.

mal hearing — understand the concept of "too loud," much less the concept of "most comfortable level." One way to train a child for this task is to associate a picture with the particular sensation. This paradigm is illustrated in Fig 1, in which the face sizes and facial expressions represent the level of sound. A small or soft sound is indicated by the small face, while the largest face with the frown indicates that the sound is too loud.

Unfortunately, there are several problems inherent in this procedure. First, we have found that most children always point to the happy face, probably because it is the most pleasant. It is possible that the child really does not equate the picture with the event because he or she does not have the conceptual ability to make the connection between the two. Second, it is possible that they will point to the pleasant face even if the sound is much too loud, indicating that they would prefer the sound at that level. A third potential problem is the basis of comparison used by the child. If the child has been a hearing aid user, he or she may try to equate the sound to that of the hearing aid and any sound louder than that experienced through the aid would be considered too loud.

Many implant audiologists have attempted to train children in degrees of loudness through exposure to changes in the degree of light or vibration. While this procedure works sometimes, such a method requires a great deal of participation and concentration by the child. Implant clinicians also rely on behavioral observation to set the upper limits of the device. After establishing minimal levels, the clinician then raises the level of input until the child begins to exhibit some sign of distress through squirming, crying, or facial expression. The stimulation then is judged to be too intense and is reduced an arbitrary amount and used as the maximum stimulation level.

Over time, good programs can be made even for very young children with these methods together with observations and input from home and school. However, overstimulation or understimulation can occur easily, leading to rejection of the device or lack of appropriate progress. The EART responses can provide a quick and relatively painless alternative for setting comfortable and appropriate upper levels in device programming.

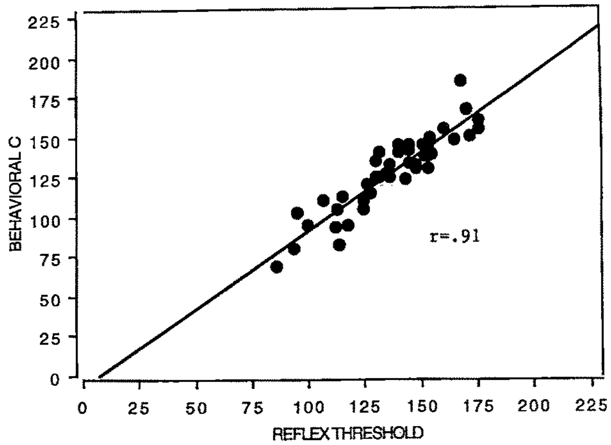


Fig 2. Scattergram illustrating strong positive relationship between electrically elicited auditory reflex threshold (EART) and upper loudness level (C level) in 40 adult cochlear implant users.

USING EART IN DEVICE PROGRAMMING

In an earlier study,[10] we reported on auditory reflexes obtained from a group of 25 postlinguistically deafened adult implant users. Of this group, 17 (68%) had measurable reflexes. In all but 2 patients, the absence of reflexes could be explained by either middle ear abnormalities or the cause of deafness, including otosclerosis and head trauma. Careful measures were made of behavioral threshold, maximum comfortable loudness level, and the level of discomfort for each of these patients. Statistical analysis showed that no relationship existed between the implant user's behavioral threshold for electrical stimulation and the middle ear muscle response. However, the lowest level at which the middle ear muscle response could be elicited was found to have a high positive relationship with both the maximum comfortable loudness level and the uncomfortable loudness level. In all cases, the middle ear muscle reflex was found to occur below the level of discomfort and was slightly above the level of maximum comfort.

Figure 2 illustrates the relationship between behaviorally determined levels of maximum comfort and threshold of the middle ear muscle reflex obtained in this study group. Moreover, upper levels set to be equal to reflex thresholds were judged to be of equal loudness by these experienced implant users. In a second series of postlinguistically deafened adult patients, programs were made by means of upper comfort levels set by EARTs. Speech perception test results then were compared to those obtained with the subject's behaviorally derived program. Speech per-

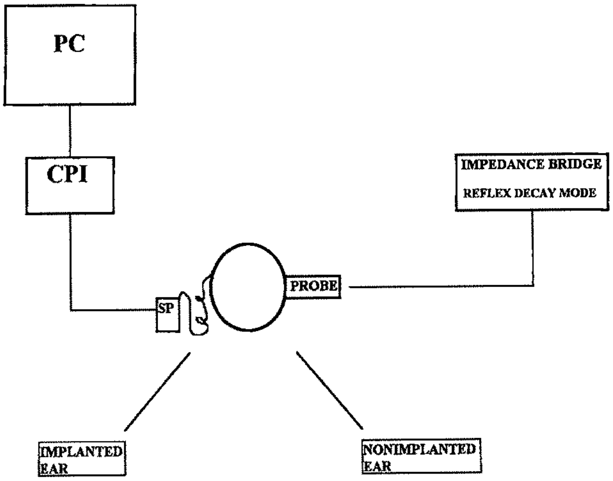


Fig 3. Schematic diagram of equipment used to measure EART responses with Clarion cochlear implant. PC — personal computer, CPI — Clinician's Programming Interface.

ception was found to be equal between the 2 programming methods. Therefore, these results suggested that EART responses could be valuable as a guide for programming young children who cannot or will not provide behavioral responses.

However, because of the potentially increased incidence of transient middle ear disorders in children, there was some concern that reflexes might be absent more often in children than in adults. Therefore, similar to the adult study, we attempted to measure reflexes in 40 children who used the Nucleus implant. At initial device programming, reflexes were present in 31 (75%) of the children. The level of maximum comfort was set on the basis of reflex threshold. Then, the maximum levels were reduced by 30% until the child was comfortable with the sound. The levels then were increased on the basis of the reaction of the child until maximum levels were set at approximately 10% below actual reflex threshold levels. Each of the children had all channels programmed during the first 2 programming days, and they were able to use the device set at the target maximum stimulation levels in less than 1 month. No child in this group on whom reflexes were obtained rejected the device. Since that study, the measurement and use of middle ear muscle reflexes has become a routine procedure for programming children in our facility.

OBTAINING EART WITH CLARION COCHLEAR IMPLANT

To date, reflexes have been obtained in 11 of 17 (65%) pediatric Clarion users ranging in age from 2 to 13 years. Reflexes were absent in 4 patients. One child refused to cooperate with the procedure, and 1 child had bilateral pressure equalization tubes.

Measurement of EARTs with the Clarion requires SCLIN for Windows, the Clinician's Programming Interface (CPI), the programming cable that connects the speech processor to the CPI, a speech processor and headpiece-cable assembly, and a commercially available immittance bridge with a reflex decay mode. Figure 3 diagrams the equipment configuration used in measurement of middle ear muscle reflexes. The SCLIN for Windows software currently in use for programming the Clarion 1.2 and S-Series processors offers an option for measuring EARTs that allows the clinician to vary multiple stimulus parameters. In addition, reflexes may be measured in the "T and M" mode of the programming screen by means of the actual programming parameters.

The first step in obtaining EART responses is to perform tympanometry. The ear of choice is the nonimplanted side. We have been able to measure EARTs successfully in the implanted ear, but have found that a response is more likely to be present in the nonimplanted ear, where measurement is somewhat less cumbersome. However, if the nonimplanted ear exhibits abnormal middle ear function, the implanted side should be used. Just as in normal-hearing individuals, reflexes cannot be obtained in implant users with abnormal middle ear function. Therefore, if tympanometry shows severely reduced compliance, a nonintact tympanic membrane, or extreme negative pressure, it is best to wait until another time to attempt reflex measurements. Nonetheless, we have measured reflexes successfully in an ear with compliance readings of 0.2 mL and in ears with negative pressures up to approximately –225 decapascals. In the 1 case of reduced compliance, a peak was present, and there was no visual indication of middle ear fluid. It was determined that the shallow compliance was most likely a normal response for this 2-year-old child. In fact, robust reflexes were obtained that have remained stable for nearly 1 year of implant use.

Once normal middle ear function has been established, the reflex decay mode is selected and middle ear pressure is equalized. There is no need for the contralateral probe, because stimuli are generated and delivered through the implant system.

To access the EART mode in the software, the clinician should select "Utilities," followed by "Options." "Objective Measures" then is selected from the options cards. From this screen, parameters such as stimulus-on and stimulus-off times, as well as interstimulus wait times and number of stimulus presentations, may be specified. Once the desired parameters have been chosen, the clinician returns to the CIS or SAS editing screen, where the EART mode is selected.

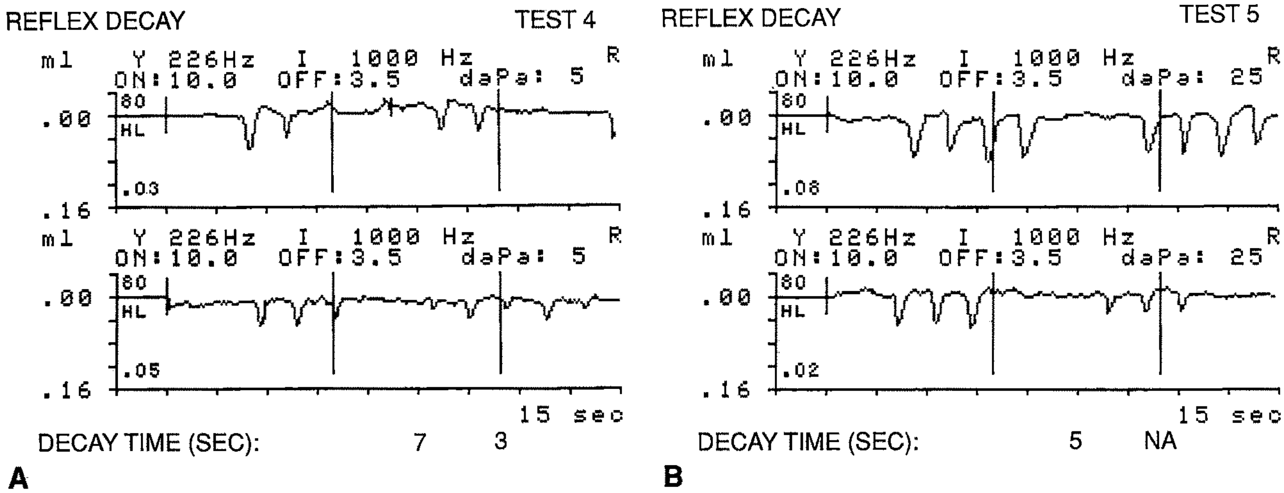


Fig 4. EART responses from 2-year-old Clarion implant user. Responses were obtained at A) initial fitting, and B) 3 months postimplantation, and were used as basis for setting initial most comfortable loudness (M) levels.

While the 10-second baseline is running, presentations of the stimuli may begin at the level determined by the clinician. It is our policy to begin stimulating at levels of approximately 100 Clinical Units and to raise the stimulus level slowly until a reflex is elicited. Stimuli are presented in series of 3 to 5 pulses. The reflex response should appear as a downward deflection in the baseline, 1 deflection for each stimulus presentation. Once a definite response is obtained, stimulus levels are decreased in fine steps until the response disappears. This level is used as the EART level. The EARTs are never determined with ascending levels, because we have found that the lowest thresholds are obtained with a descending paradigm. The last visible response on the descent provides the most repeatable and stable EART. If the child shows any sign of distress before an EART is established, stimulation of another channel is attempted. If no response is obtained on the second channel, the procedure is terminated.

Figure 4 shows a series of EARTs obtained from a 2-year-old Clarion user. The EARTs were obtained during the initial stimulation. Three programs were made. In 1 program, M levels were set at 90% of the EART levels. In the other 2 programs, M levels were further reduced from the EART: 1 at 80% and 1 at 70%. The parent was asked to have the child use the program with the lowest M levels (70%) first. After several days, when the child began tolerating the sound with no difficulty, the program was changed to the 80% level. After approximately 3 weeks, the child was using the 90% program with no sign of discomfort or distress. At 3 months, EARTs were remeasured and found to have increased slightly. A program at 90% of the new levels was made and tolerated with no difficulty. The EART levels have remained stable in the succeeding 5 months. The child wears the device consistently and is making excellent progress.

CONCLUSIONS

Measuring EART responses in Clarion cochlear implant users is quick and simple. When an EART response is present, the clinician can be assured that an auditory percept is present and that the sound is loud, but not uncomfortable. The clinician then may use the EART level as a basis for conditioning a response in children who exhibit no consistent behavioral responses to electrical stimulation. In addition, the EART can be used as a guideline for setting the M levels.

REFERENCES

1. Battmer R, Laszig R, Lehnhardt E. Electrically elicited stapedius reflex in cochlear implant patients. Ear Hear 1990;11: 370-4.

2. Shallop JK, Beiter AL, Goin DW, Mischke RE. Electrically evoked auditory brainstem responses (EABR) and middle latency responses (EMLR) obtained from patients with the Nucleus multichannel cochlear implant. Ear Hear 1990;11:5-15.

3. Kileny PR. Use of electrophysiologic measures in the management of children with cochlear implants: brainstem, middle latency, and cognitive (P300) responses. Am J Otol 1991;12 (suppl 12):37-42.

4. Brown CJ, Abbas PJ, Fryauf-Bertschy H, Delsay D, Gantz BJ. Intraoperative and postoperative electrically evoked auditory brainstem responses in Nucleus cochlear implant users: implications for the fitting process. Ear Hear 1994;15:168-76.

5. Spivik LG, Chute PM, Popp AL, Parisier SC. Programming the cochlear implant based on electrical acoustic reflex thresholds: patient performance. Laryngoscope 1994;104:1225-30.

6. Spivik LG, Chute PM. The relationship between electrical acoustic reflex thresholds and behavioral comfort levels in

children and adult cochlear implant patients. Ear Hear 1994; 15:184-92.

7. Hodges AV, Ruth RA, Lambert PR, Balkany TJ. Electric auditory brainstem responses in Nucleus multichannel cochlear implant users. Arch Otolaryngol Head Neck Surg 1994;120: 1093-9.

8. Jerger J, Fifer R, Jenkins H, Mecklenburg D. Stapedius reflex to electrical stimulation in a patient with a cochlear implant. Ann Otol Rhinol Laryngol 1986;95:151-7.

9. Jerger J, Chmiel R, Oliver T. Prediction of dynamic range from stapedius reflex in cochlear implant patients. Ear Hear 1988;9:4-8.

10. Hodges AV, Balkany TJ, Ruth RA, Lambert PR, Dolan-Ash MS, Schloffman JJ. Electrical middle ear muscle reflex: use in cochlear implant programming. Otolaryngol Head Neck Surg 1997;111:255-61.

Ann Otol Rhinol Laryngol 108:1999

SIMULTANEOUS ANALOG STIMULATION (SAS)–CONTINUOUS INTERLEAVED SAMPLER (CIS) PILOT COMPARISON STUDY IN EUROPE

ROLF D. BATTMER, PHD
PHILIP HAAKE, MD
YITZAK ZILBERMAN
THOMAS LENARZ, MD, PHD
HANNOVER, GERMANY

The recent availability of the enhanced bipolar electrode array in the CLARION® Multi-Strategy™ Cochlear Implant has permitted clinicians to fit patients successfully with the Simultaneous Analog Stimulation (SAS) strategy by means of bipolar coupling. Out of 22 consecutively implanted subjects, 20 subjects could be fitted with both Continuous Interleaved Sampler (CIS) and SAS strategies. Their performance was evaluated up to 3 months postoperatively. Speech perception results, as well as the patient's preference for either CIS or SAS, were examined. It was found that half of the subjects selected SAS as their preferred strategy and that the use of a preferred strategy resulted in higher overall patient performance. Further analyses showed that those subjects preferring SAS had higher electrode impedance values and lower threshold and most comfortable loudness levels than subjects preferring CIS. We presume that these psychophysical findings are, in part, related to the position of the intracochlear electrode array. Specifically, SAS users may have a more modiolus-hugging electrode array position.

KEY WORDS — cochlear implant, continuous interleaved sampler, simultaneous analog stimulation.

INTRODUCTION

The development of nonsimultaneous pulsatile speech processing strategies, such as Continuous Interleaved Sampler (CIS)[1] and SPEAK,[2] has led to improved speech understanding in patients using cochlear implants. This finding raised the question of whether performance could be further improved with other speech processing techniques. An alternative to nonsimultaneous pulsatile speech processing strategies is a simultaneous analog stimulation. The compressed analog (CA) strategy[3] is an example of this type of strategy that was used with the Ineraid device. The analog strategy allows a more accurate and natural representation of temporal cues, as compared to pulsatile stimulation, which more accurately conveys spectral information. During the development of CIS, its performance was compared to CA as implemented in the Ineraid device. Speech test results with CIS proved to be almost always superior to those with CA.

Unfortunately, the Ineraid device only allowed CA and CIS to run in *monopolar* mode. CIS could not be compared with *bipolar* CA, because the coupling mode could not be changed. Initial attempts to provide CLARION® Multi-Strategy™ Cochlear Implant users with a bipolar CA strategy failed, because adequate loudness growth could not be achieved in most patients. The cause of this interaction was most likely due to the small distance between the 2 bipolar contacts on the Clarion electrode array. This arrangement resulted in a very restricted electrical field. The excited neural population was not sufficient to ensure loudness growth, even at a maximum current output level.

The recent introduction of the enhanced bipolar coupling mode with the Clarion cochlear implant has made it possible to fit patients with a simultaneous processing strategy. The "enhanced bipolar" mode (Fig 1) combines bipolar pairs in such a way that a medial contact is paired with the next lateral contact (ie, medial 1 with lateral 2, medial 2 with lateral 3). With this configuration, the distance between the pairs is 3 times greater, allowing for a more distributed electrical field that enables better loudness growth. This coupling arrangement reduces the number of

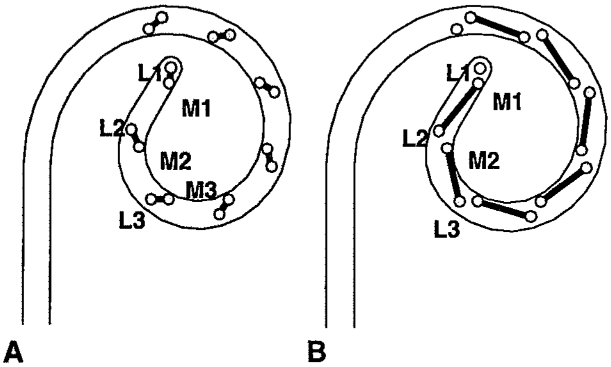


Fig 1. A) Bipolar and B) enhanced bipolar coupling modes. L — lateral contact of bipolar pair; M — medial contact of bipolar pair.

From the Department of Otolaryngology, Medizinische Hochschule Hannover, Hannover, Germany.
CORRESPONDENCE — Rolf D. Battmer, PhD, Dept of Otolaryngology, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, D-30265, Hannover, Germany.

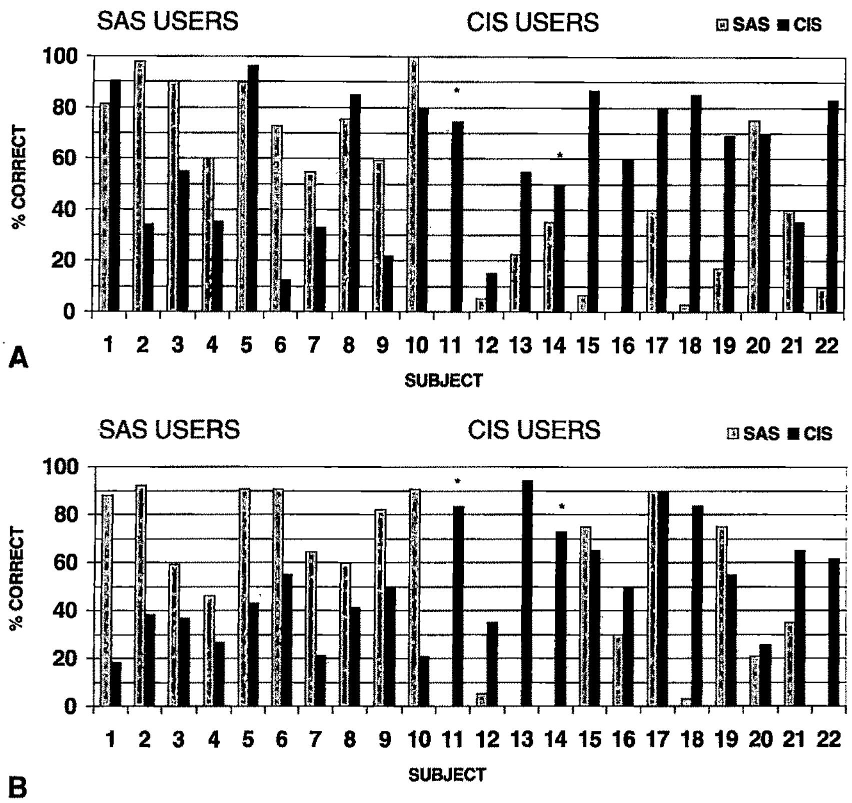


Fig 2. Test results of Simultaneous Analog Stimulation (SAS; subjects 1 through 10) and Continuous Interleaved Sampler (CIS; subjects 11 through 22) groups for number and sentence tests after A) 2 weeks and B) 3 months. Asterisk indicates 2 subjects who could not be fitted with SAS. While majority of SAS users do well in their nonpreferred listening mode, most of CIS users could not undergo testing with SAS.

enhanced bipolar channels to 7. To differentiate the new arrangement from the older, monopolar-coupled CA, the speech-processing strategy utilizing the enhanced coupling is now referred to as Simultaneous Analog Stimulation, or SAS.

When enhanced bipolar Clarion devices became available, a clinical study was designed at the Medical University of Hannover (Medizinische Hochschule Hannover; MHH) to compare the 2 strategies, with emphasis on clinical utility. The investigation of speech test results with SAS was possible only with Clarion patients, because it is the only device that allows fitting of both the CIS and SAS strategies in the same patient.

METHODS

Patients. Twenty-two postlingually deafened German-speaking adults took part in the study. All patients had a fully inserted electrode array, with the benefit of all 16 electrode contacts. The 22 patients were implanted consecutively with the enhanced bipolar device. Subjects in the study were fitted with both the CIS and SAS strategies at the beginning of their rehabilitation period, which was 2 weeks after implantation. Equal training time with the speech therapists was allotted to both strategies. The subjects' objective performance over time with both SAS and CIS was evaluated. A subjective preference for one strategy over time also was investigated. The relationship between objective test results and subjective preference then was compared.

Subjective Evaluation. The evaluation included a patient's diary, a questionnaire, and various speech tests. Test sessions took place 2 weeks, 6 weeks, and 3 months after initial fitting. Patients had to train with both strategies. When at home, they were told to change strategies on a regular basis and to write down their experiences in the diary. The diary contained questions regarding the usefulness of the strategies in different acoustic environments, the sound quality of each strategy, and other listening experiences.

The test materials included a consonant, vowel, and monosyllable word test, as well as 3 other commonly used German tests: the number test (part of the "Freiburger Inventar"), the "Innsbrucker" sentence test, and the "Göttinger" sentence test. These tests have different levels of difficulty; therefore, it was possible to use a test appropriate for each individual's skill level at each test session. The sentence tests were delivered under no-noise, 15-dB–signal-to-noise ratio, and 10-dB–signal-to-noise ratio conditions. All stimuli were presented from a compact disk player connected directly to the speech processor.

The subject's psychophysical abilities, including T and M levels, also were evaluated and compared to speech perception results. For comparisons between groups, a nonparametric Wilcoxon test of significance was applied. When comparing within a

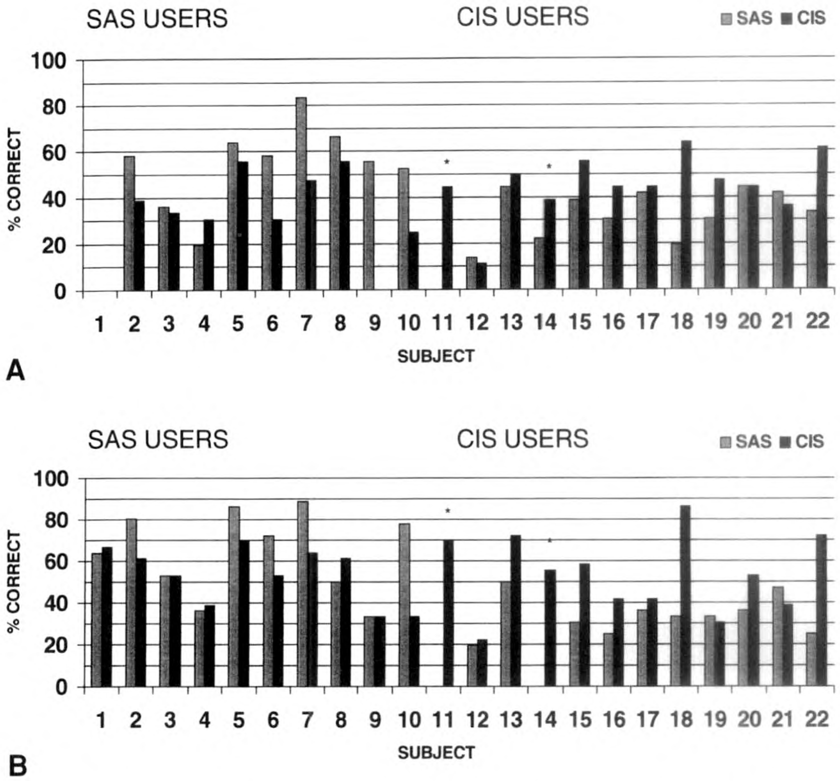


Fig 3. Results of consonant tests after A) 2 weeks and B) 3 months.

group, a Wilcoxon paired test was used. The significance level used was .05.

RESULTS

Twenty of the of 22 subjects could be fitted with both SAS and CIS. One subject could not be fitted with SAS due to insufficient loudness growth, while another dropped out following refitting after 6 weeks with M levels on 3 channels out of range.

Subjective Evaluation. After rehabilitation, 10 patients reported that SAS sounded more natural and comfortable, 9 reported this same experience for CIS, and 1 was undecided. After 3 months, 1 SAS user changed to CIS, and the undecided subject chose SAS. Thus, 50% of the subjects preferred SAS (SAS group) and 50% preferred CIS (CIS group). The daily usage time of each strategy was dependent on the preference. More than 75% of the patients reported that they used their preferred strategy most of the time, except for short periods of trying the other strategy.

In general, patients did not report that one strategy was louder than the other. About one half of the patients in both groups recognized background noise when using the nonpreferred strategy. The SAS group rated the sequential strategy slightly better than the CIS groups rated the analog strategy. The subjects tended to use their preferred strategy for all environmental sound conditions. Twelve subjects reported that the SAS strategy had a deeper sound character than CIS, while 2 subjects said that the CIS strategy had deeper pitches.

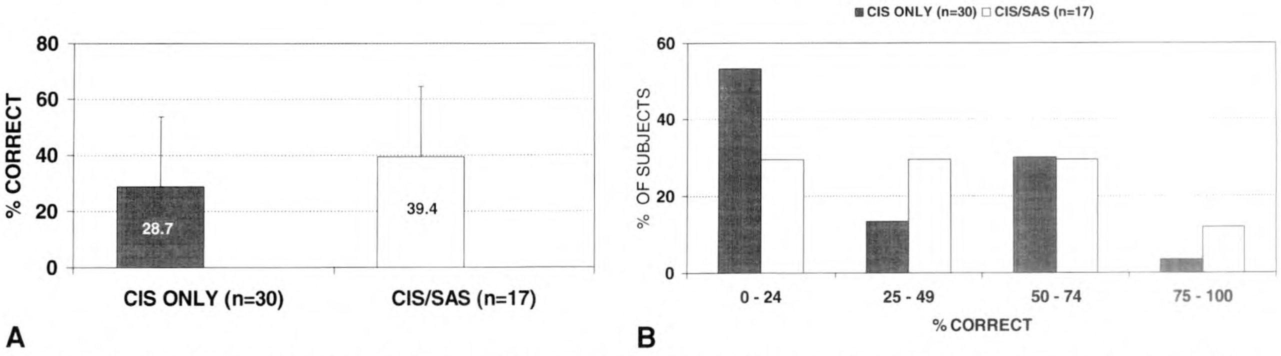


Fig 4. Results of Freiburger monosyllable word test at 3 months. A) In comparing group of subjects who were fitted with CIS only and study group receiving CIS and SAS (CIS/SAS), CIS/SAS group scores in their preferred listening mode were significantly higher. B) Distribution of scores in quartiles shows trend toward higher scores for CIS/SAS group.

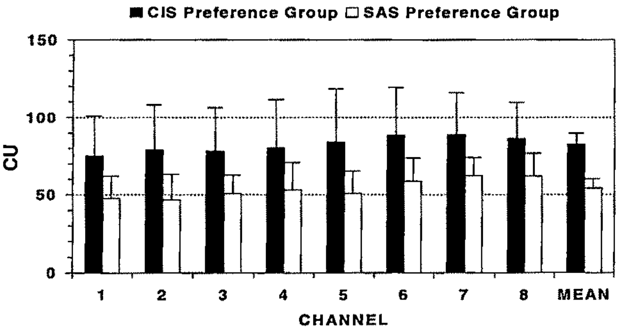


Fig 5. Threshold (T) levels of CIS and SAS groups (monopolar coupling). Pulsatile levels are shown, because all subjects could be tested in this mode. Note that difference in T and M levels between CIS and SAS users for analog is similar to difference in pulsatile mode. CU — Clinical Units (arbitrary current level).

Sentence-Number Test. The 2-week and 3-month results for the sentence and number tests, in quiet, are displayed in Fig 2. Subjects who preferred the SAS strategy are shown as numbers 1 through 10, and those preferring CIS as numbers 11 through 22. The 2 subjects who could not be fitted with SAS are marked with an asterisk. Unfortunately, the SAS group could not be compared directly with the CIS group, because subjects in each group had different levels of speech understanding and were evaluated with different test materials. Both groups performed better with their preferred strategy under all noise conditions at the 2-week test session. The difference in performance with the preferred and nonpreferred strategies was significant after 3 months. This performance difference also was the result of greater experience with the preferred strategy.

Consonant Test. Figure 3 shows the results of the consonant confusion test at the 2-week and 3-month test intervals. The results are less uniform and not as strongly related to preference as are the sentence test results. The SAS group performed significantly better with their preferred than with their nonpreferred strategy when tested after rehabilitation and after 6 weeks. The CIS group was significantly better with the CIS strategy than with the SAS strategy at every test session.

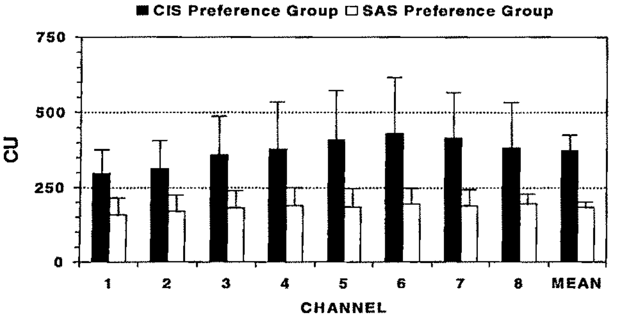


Fig 6. Most comfortable (M) levels of CIS and SAS groups. Pulsatile stimuli; monopolar coupling

Vowel Test. For the vowel test, both groups performed better with their preferred strategy at each session. However, the differences between strategies were not significant for the CIS group. The SAS group performed significantly better with the SAS strategy compared to the CIS group with the CIS strategy at each test session.

Monosyllable Word Test. Figure 4 shows the results of the monosyllable word test at 3 months. A comparison was made between the subjects in this study and the previous 30 subjects consecutively implanted at MHH. Group 1 shows the 3-month results from these 30 users who started with the 1.2 speech processor, and *only* had the choice of CIS (ie, before enhanced bipolar coupling became available). Group 2 shows the results of the first 17 subjects from this study, who had the choice between SAS and CIS. (Data from the other 3 subjects were unavailable at the time of writing.) This comparison clearly demonstrates the improvement in performance for the group that had a choice of strategies compared to the subjects who could use only CIS. The group mean scores were significantly different for group 1 and group 2 (Fig 4A). The results also are shown as percent correct scores in quartiles. The percentage of group 2 users scoring in the lowest quartile is diminishing, while the percentage of group 2 subjects scoring in the top 2 quartiles is increasing (Fig 4B). These results demonstrate that use of the preferred speech processing strategy results in higher overall subject performance.

Performance in Noise. Within each group, the differences between the no-noise and 15 dB signal-to-noise ratio conditions, as well as between 15-dB and 10-dB signal-to-noise ratios, were calculated. This comparison was made because some SAS users subjectively reported a decrease in performance in noise with SAS. It was found that at 2 weeks and at 3 months, the SAS group had a slightly larger performance drop in noise when using the SAS strategy

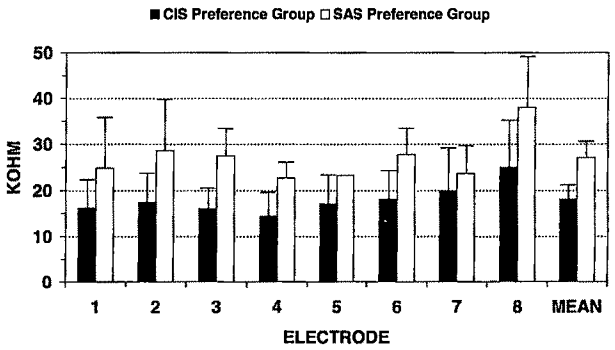


Fig 7. Electrode impedances of CIS and SAS groups. Electrode impedance values are *higher* for SAS group compared to CIS group, even though T and M levels are lower for SAS group.

compared to the CIS group using the CIS strategy.

Psychophysical Data. Following the observation that subjects displayed a strong preference for one strategy over the other, psychophysical data for the SAS and CIS groups were investigated. Figures 5 and 6 show the pulsatile stimuli threshold (T) and most comfortable (M) levels for the SAS and CIS preference groups. The T levels of subjects who preferred CIS are significantly higher than the T levels of subjects who preferred SAS. The same trend is seen for the M levels. Electrode impedance data also were evaluated (Fig 7). Subjects preferring SAS had significantly higher impedances compared to subjects preferring CIS.

DISCUSSION

This study investigated speech understanding and psychophysical measures for 22 patients fitted with both the CIS and SAS strategies. Of the 22 study subjects, 20 could be properly fitted with both Clarion SAS and CIS speech processing strategies. Ten subjects preferred CIS, while 10 preferred SAS. The SAS subjects demonstrated good speech test results with both CIS and SAS, while the CIS users had good results only from CIS. When comparing the Clarion subjects in this study (having the choice of CIS or SAS) with Clarion subjects who only had access to CIS, we found that the group having the choice of strategy had higher overall performance.

A very interesting and important finding from this study was that the subjects preferring SAS had significantly higher electrode impedances and lower threshold (T) and most comfortable (M) levels than the CIS users. A similar finding was described by Reuter et al[4] in an animal model. One possible explanation for this phenomenon is the position of the electrode array. If the electrode array is lying laterally in the scala tympani, there is perilymph between the electrode contacts and the medial wall. Stimulation current will spread through this fluid layer, coming into contact with a larger surface area of the bony walls, through which it may find many paths to spread through the cochlea. This current dispersion may result in low electrode impedance values. Because only a few of the paths intersect the spiral ganglion, more stimulation current must be applied to recruit enough auditory neurons to reach threshold. However, if the electrode array is positioned close to the medial wall, most of the current will pass through the adjacent medial wall of the scala tympani and thus into the spiral ganglion. This restricted pathway results in relatively large electrode impedance values, but the applied currents are directed more efficiently to recruiting the local auditory neurons, thereby resulting in lower thresholds. Researchers at MHH are examining the radiographs and computed tomography scans of patients fitted with CIS and SAS to determine if a relationship between electrode position and strategy preference exists.

CONCLUSION

The availability of both simultaneous analog and sequential pulsatile speech processing strategies offers greater opportunity for achieving improved patient performance and increased overall benefit. The psychophysical data suggest that individuals who prefer SAS may have an electrode position closer to the medial wall, thereby leading to better channel separation. Therefore, further investigations of CIS and SAS users may lead to an improved electrode design, facilitating the development of new and more effective speech processing strategies with lower power consumption.

The natural process of hearing is extremely complex. The primary function of a cochlear implant is to transform mechanical energy into bioelectrical signals that can be transmitted along the auditory nerve. At the same time, the implant must compensate for individual neurologic deficits. A solution to this problem is to offer a variety of different speech processing strategies that can be adapted to different levels of impairment. The results of this study would support such an approach.

REFERENCES

1. Wilson BS, Finley CC, Lawson DT, Wolford RD, Zerbi M. Design and evaluation of a continuous interleaved sampling (CIS) processing strategy for multichannel cochlear implants. J Rehabil Res Dev 1993;30:110-6.

2. McDermott HJ, McKay C, Vandali AE. A new portable sound processor for the University of Melbourne/Nucleus Limited multielectrode cochlear implant. J Acoust Soc Am 1992;91:3367-71.

3. Eddington DK, Dobelle WH, Brackmann DE, Mladejovsky MG, Parkin JL. Auditory prostheses research with multiple channel intracochlear stimulation in man. Ann Otol Rhinol Laryngol [Suppl] 1978;87(suppl 53).

4. Reuter G, Cords SM, Issing P, Lenarz T. Measurements of threshold shifts observed when using normal and preformed electrodes. Am J Otol 1997;18(suppl 6):S26.

Ann Otol Rhinol Laryngol 108:1999

SAS-CIS PREFERENCE STUDY IN POSTLINGUALLY DEAFENED ADULTS IMPLANTED WITH THE CLARION® COCHLEAR IMPLANT

MARY JOE OSBERGER, PHD LAUREL FISHER, PHD
SYLMAR, CALIFORNIA

This study examined the speech perception performance of 71 postlingually deafened adults implanted with the CLARION® Multi-Strategy™ Cochlear Implant. After 3 months of implant use, one third of the patients (n = 23) preferred to use the Simultaneous Analog Stimulation (SAS) strategy, and two thirds of them (n = 48) chose to use the Continuous Interleaved Sampler (CIS) strategy. The mean CID sentence scores were similar for the SAS and CIS user groups at the 3-month postoperative interval. In contrast, the mean CNC word score of the SAS users was significantly higher than the mean score of the CIS users after 3 months of implant experience. Patients who preferred to use SAS demonstrated significantly shorter duration of deafness at time of implantation than did the CIS users, whereas the CIS users demonstrated significantly higher preoperative sentence recognition scores than the SAS users. The results suggested that access to a preferred processing strategy improved the overall group performance of postlingually deafened adults in the present study compared to the results of previous studies in which only the CIS strategy was available to most patients with the Clarion.

KEY WORDS — cochlear implant, continuous interleaved sampler, postlingually deafened adults, simultaneous analog stimulation.

INTRODUCTION

Since its inception, the CLARION® Multi-Strategy™ Cochlear Implant has offered the ability to implement distinctly different speech processing strategies, ranging from fully simultaneous analog stimulation to high-rate sequential pulsatile sampling, with any type of waveform, and the option of monopolar or bipolar electrode coupling. The Clarion's flexible design was conceived to accommodate newer and more effective speech processing strategies as they are developed and to offer the option of different strategies to each individual user.[1,2]

During recent years, however, research in cochlear implant speech processing has emphasized only 1 type of strategy: nonsimultaneous (sequential) pulsatile processing (eg, SPEAK, Continuous Interleaved Sampler [CIS]).[3,4] Nonsimultaneous strategies evolved to reduce channel interaction, or random interference resulting from the spread of current from the targeted nerve population to neighboring nerves. Channel interaction degrades channel independence and affects the salience of channel-related speech cues, adversely affecting speech understanding.[5] Nonsimultaneous strategies reduce channel interaction by stimulating adjacent or nearby channels sequentially rather than simultaneously.

The temporal pattern of stimulation (ie, simultaneous or nonsimultaneous), however, is not the only factor to be considered in reducing current spread and its negative effect on spatial selectivity and speech discrimination. Of equal importance is the stimulation mode (ie, monopolar or bipolar) and the neural interface or electrode design. In monopolar stimulation, multiple active electrodes share a distant ground and, therefore, cause a broad spread of current and pattern of excitation. Monopolar stimulation can be used with nonsimultaneous strategies such as CIS because only 1 electrode is stimulated at a time. Effective use of simultaneous strategies, however, cannot be achieved with monopolar stimulation, due to the channel interaction that arises when more than 1 electrode is stimulated at the same time. In the classic study by Wilson et al,[3] patients who were implanted with the Ineraid device achieved significantly higher speech recognition scores with a nonsequential, pulsatile speech processing strategy (CIS) than with a simultaneous analog (Compressed Analog [CA]) scheme.[3] Patients in this study, however, had access only to a monopolar mode of stimulation. Thus, it is not surprising that performance was superior with the strategy that allowed for more effective reduction of channel interaction (ie, a nonsimultaneous one) when it was employed with this electrode configuration.

Bipolar stimulation, in which each active electrode in a multielectrode array is paired with another electrode that is in close proximity, provides more spatially selective stimulation than monopolar stimulation and therefore is the mode of choice with a simultaneous strategy. Moreover, bipolar stimulation may limit or eliminate the negative effects of channel interaction that occur during simultaneous stimulation when it is used with an electrode designed to be high-

---

From Advanced Bionics Corporation, Sylmar, California.

CORRESPONDENCE — Mary Joe Osberger, PhD, Advanced Bionics Corporation, 12740 San Fernando Rd, Sylmar, CA 91342.

ly selective, such as the Clarion electrode.[6] The Clarion electrode is designed to follow the spiral shape of the cochlea. The modiolar-hugging properties cause its small contacts to be oriented toward and positioned near the medial wall of the scala tympani, where the spiral ganglion cells — the neural elements responsive to electrical stimulation — are located.

During the Clarion clinical trial with postlingually deafened adults initiated in 1991, patients were fitted with a nonsimultaneous strategy (CIS) and a simultaneous strategy (CA) and offered the option of using 1 or both schemes in their speech processors. The results revealed that 95% of the patients preferred the nonsimultaneous, CIS strategy, whereas only 5% chose to use the simultaneous, CA speech processing scheme.[1,7] This preference pattern occurred because the electrode contacts were closely spaced in a radial-bipolar orientation in the Clarion's original electrode (referred to as the 1.2 electrode). Although this arrangement achieved a high degree of spatial selectivity, it required greater current levels to achieve adequate loudness growth than the system permitted. Thus, the only stimulation mode with which patients could achieve adequate loudness growth was monopolar. Because of the channel interaction and poor speech understanding that occurred with the use of monopolar stimulation with the simultaneous CA strategy, most patients preferred the nonsimultaneous CIS strategy.

Although excellent results have been obtained with CIS with the Clarion,[7] there are distinct advantages to a simultaneous analog strategy if channel interaction can be effectively reduced. Simultaneous analog processing provides the most faithful reproduction of incoming sound and most closely approximates the pattern of stimulation experienced by the normal-hearing ear. Moreover, the amplitude of the output signal is updated on each channel 10 times more frequently with the Clarion's simultaneous analog processing than with the sequential CIS strategy, thereby preserving fine temporal details in the acoustic input signal. At this time, there have been no studies of patient performance with a simultaneous speech processing strategy when it has been optimally implemented with bipolar stimulation. Until such studies are conducted, the efficacy of simultaneous analog speech processing is unknown.

This study examined adult patients' preference for a simultaneous analog strategy, implemented with bipolar stimulation, or a nonsimultaneous pulsatile strategy, implemented with monopolar stimulation. The study was initiated following regulatory approval of a modification in the Clarion electrode that facilitated adequate loudness growth with a bipolar electrode configuration. The specific goals of the study were 1) to determine the proportion of patients that preferred to use the simultaneous strategy, the nonsimultaneous strategy, or both strategies, and 2) to examine the speech perception performance of patients using their preferred strategy.

METHODS

Electrode Modification. A hardware change was implemented in the Clarion's bipolar electrode coupling to allow access to bipolar stimulation and simultaneous strategies for a greater number of patients implanted with the Clarion. In the modified electrode, referred to as the "S-Series" electrode (formerly called the "enhanced bipolar electrode"), the medial and lateral contacts are paired diagonally rather than radially, increasing the distance between the contacts in a bipolar pair, as shown in Fig 1. Thus, a larger population of nerves is excited at each stimulation site, reducing the current level required to achieve loudness growth. To distinguish between the 8-channel analog strategy implemented with the former standard 1.2 electrode, termed compressed analog (CA), the new 7-channel bipolar strategy is called SAS. The latter is implemented with the diagonal pairing of electrodes in the S-Series implant. Monopolar stimulation, as in CIS, is unaffected by either of the bipolar electrode coupling arrangements and retains 8 active channels. All patients in this study were implanted with the S-Series implant and electrode.

Subjects. Inclusion criteria for enrollment in the study consisted of profound, bilateral, sensorineural hearing loss (ie, 3-frequency pure tone average ≥ 90 dB hearing level [HL]); negligible hearing aid benefit; postlingual onset of deafness; no previous implant experience; English proficiency; normal cognitive function; and willingness to participate in the study. In this report, results will be presented for the first 71 patients who met these criteria and who also had been evaluated at the first postoperative interval (ie, 3 months following initial stimulation).

The patients were recruited from 11 investigational sites. The mean age at implantation was 56 years (SD = 17), with a mean age at onset of deafness in the ear implanted of 43 years (SD = 23), and a mean duration of deafness in the ear implanted of 13 years (SD = 15). The mean preoperative unaided pure tone average in the implanted ear was 104 dB HL (SD = 14).

Procedures. Patients received their Clarion speech processor at the initial stimulation session, approximately 4 to 6 weeks following surgery. The first 19 patients received the 1.2 speech processor, whereas

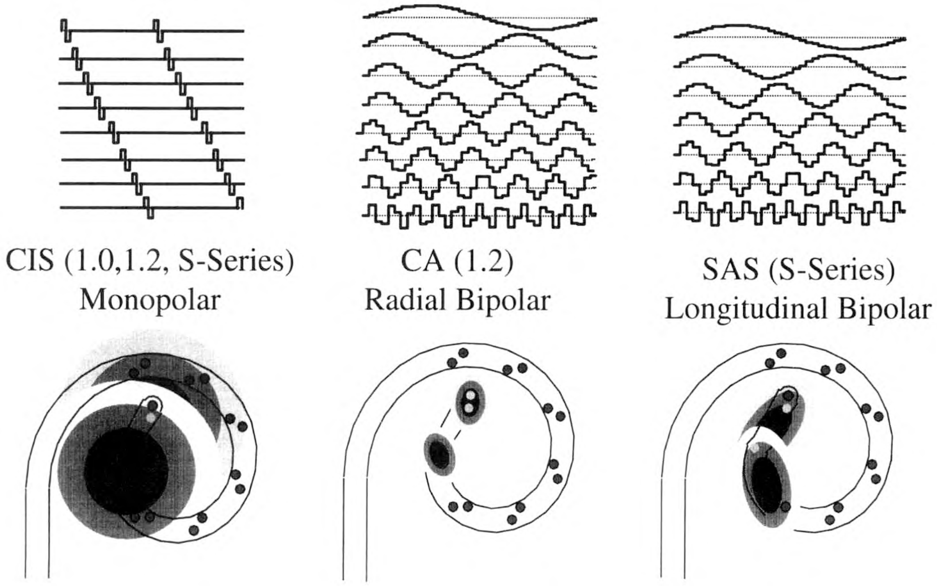


Fig 1. Schematic of stimulation mode, processing strategy, and temporal pattern of waveform stimulation of Clarion devices.

the subsequent 52 patients received the S-Series speech processor, which was introduced after the initiation of the study. The SAS strategy was fitted with bipolar stimulation, and the CIS strategy with monopolar stimulation. The protocol specified that both strategies should be fitted on the same day and that the order of fitting should be alternated across patients at each center. Patients were instructed to use each strategy as often as possible in a variety of everyday listening situations. Programming adjustments were made after 3 months of implant use and at interim sessions depending on the needs of each patient.

Speech recognition performance was evaluated with sentences and monosyllable words preoperatively and postoperatively after 3 months of implant use. Preoperatively, the measures were administered in the best-aided condition to establish implant candidacy and for later comparison with postoperative scores. The tests were administered postoperatively while the patients were using their preferred strategy (ie, SAS or CIS). Stimuli were presented at 70 dB sound pressure level in the sound field as measured at the microphone of each patient's hearing aid (preoperatively) or implant (postoperatively).

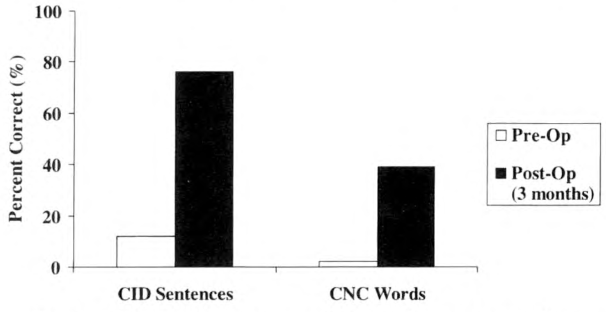


Fig 2. Mean preoperative and 3-months-postoperative scores (percent correct) on CID sentence test and CNC monosyllable word test for 71 patients implanted with S-Series implant.

Open-set sentence recognition was assessed with the CID test[8] with the compact disk (CD) recording distributed by Cochlear Corporation.[9] On this CD, the 10 lists of 10 sentences appear as 5 lists of 20 sentences, with 3 practice sentences at the beginning of each 20-sentence list. Performance is scored as the percentage of key words correctly understood in the 20 sentences (ie, 100 per 20 sentences).

Open-set word recognition was assessed with the CNC (Consonant-Nucleus-Consonant) test.[10] This test consists of monosyllable words with equal phonemic distribution across lists, with each list exhibiting approximately the same phonemic distribution as the English language. The CNC lists were later revised to eliminate relatively rare words and proper nouns.[11] The resulting 10 lists of 50 words contain monosyllabic words with a frequency of occurrence greater than 4 per million, as calculated in the Thorndike and Lorge word frequency tables. The CD recording of the CNC words from the Minimum Speech Test Battery for Adult Cochlear Implant Users[12] was employed in the study. There are 3 practice words at the beginning of each list. Each word is preceded by the carrier word "ready." Performance is scored as the percentage of words correctly repeated.

RESULTS

At the 3-month postoperative evaluation, all patients expressed a preference for either SAS or CIS. Twenty-three (23) patients, or 32% of the study group, preferred SAS, and 48 patients, or 68% of the group, preferred CIS. Figure 2 shows the mean

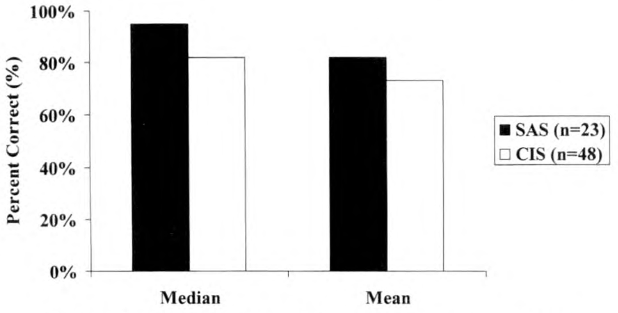


Fig 3. Median and mean CID sentence scores (percent correct) after 3 months of implant use for patients who preferred to use SAS (n = 23) or CIS (n = 48).

preoperative CID sentence and CNC word scores for all 71 patients compared to the 3-month postoperative scores with their Clarion implants. There was a significant difference between the mean preoperative and postoperative scores on the CID test (t(60) = –15.5, p <. 001) and the CNC test (t(60) = –13.5, p < .001). (Preoperative data were missing for some patients.)

The mean preoperative CID score was 12% (SD = 18), and the 3-month postoperative score was 76% (SD = 30). The median CID score after 3 months of implant use was 90%, indicating that half of the patients achieved a score of 90% or higher after this limited period of implant experience. Preoperatively, the mean CNC word score was 2% (SD = 4), whereas the mean and median scores after 3 months of implant use were 39% (SD = 23) and 38%, respectively.

Figure 3 shows the mean and median sentence scores for the SAS and CIS users. There was no significant difference between the mean CID scores of the SAS and CIS users (t(44) = –1.2 , p = .30). The mean sentence score on the CID test for the 23 patients who preferred and were tested with SAS was 82% (SD = 30), compared to a mean score of 73% (SD = 30) for the 48 patients who preferred and were evaluated with CIS. The median CID sentence score for the SAS users was 95%, compared to a median score of 82% for the CIS users.

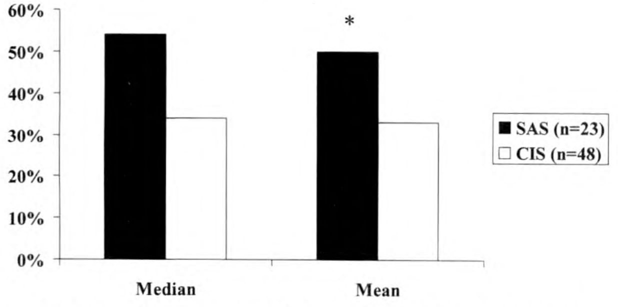


Fig 4. Median and mean CNC monosyllable word scores (percent correct) after 3 months of implant use for patients who preferred to use SAS (n = 23) or CIS (n = 48). * — p = .007.

PREOPERATIVE DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WHO PREFERRED TO USE SAS OR CIS SPEECH PROCESSING STRATEGY

Variable	*SAS Users (n = 23)*	*CIS Users (n = 48)*
Age at implantation (y)	55 ± 17	57 ± 17
Age at onset of deafness (y)	47 ± 20	42 ± 24
Duration of deafness (y)	8 ± 9	15 ± 17
Unaided pure tone average (dB hearing level)	99 ± 14	106 ± 13
CID sentence score (%)	6 ± 12	15 ± 20
CNC word score (%)	1 ± 2	2 ± 4

Data are mean ± SD.

Figure 4 shows the mean and median scores on the CNC test for the SAS and CIS users after 3 months of implant use. There was a significant difference between the CNC word scores of the SAS and CIS users at the 3-month interval (t(34) = –2.8, p = .007). The mean score of the SAS users was 50% (SD = 25), and the median score was 54%. The mean score of the CIS users was 33% (SD = 19), with a median score of 34%.

Preoperative demographics of the patients who preferred SAS and those who preferred CIS were examined to determine if there was a relationship between patient characteristics and preferred strategy. As shown in the Table, the characteristics of the SAS and CIS users were similar, with 2 exceptions. Patients who preferred SAS had significantly shorter duration of the deafness at the time of implantation than the CIS users (t(65) = 2.1, p = .04). Also, patients who preferred CIS had significantly higher preoperative sentence recognition scores than did the SAS users (t(56) = 2.1, p = .04).

The results of this study were compared to those of previous studies in which the majority of patients had access to only the CIS strategy. In 1 study, adult patients were implanted with the larger 1.0 device and electrode, whereas in a subsequent study, pa-

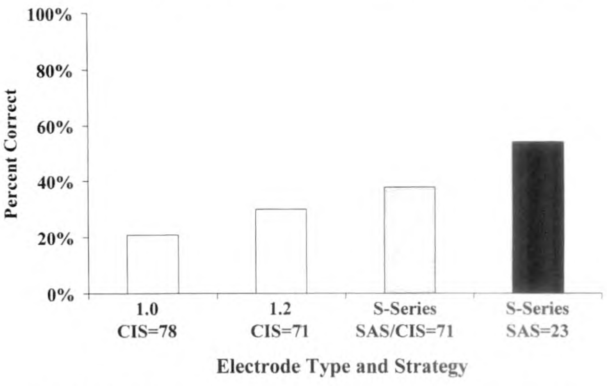


Fig 5. Median monosyllable word scores (3 months postoperatively) for postlingually deaf adults implanted with Clarion cochlear implant as function of electrode type and speech processing strategy.

tients received the smaller 1.2 device and electrode.[1,7] The only difference between these devices was the size of the receiver-stimulator, which was made smaller in the 1.2 version for the pediatric population. Patients with the 1.0 device, however, received the older 1.0 speech processor, whereas patients who were implanted with the 1.2 device received the 1.2 speech processor. Previous results showed an increase in patient performance with the 1.2 processor, resulting from improvements in hardware and software upgrades, as well as to improvements in the fitting system. In contrast, differences between the 1.2 and S-Series speech processors were largely cosmetic and were not predicted to impact patient performance. Patient inclusion criteria were the same for the 1.0 and 1.2 studies, as well as for the current investigation.

Figure 5 shows the median monosyllable word recognition scores for patients in the 3 studies. Results from the previous 2 studies are shown only for those patients who preferred and were tested with CIS (n = 78 with the 1.0 device; n = 71 with the 1.2 device). The results suggest a trend of higher performance with technological improvements. As noted above, differences between the patients with the 1.0 and 1.2 devices are due to largely to speech processor improvements. However, the difference between the results of the patients with the 1.2 device and those of the patients with the S-Series implant presumably reflects improvement resulting from access to different speech processing strategies that existed for the patients in the current study. The median word scores (NU6 test) of the patients who used CIS with their 1.0 and 1.2 speech processors were 21% and 30%, respectively, compared to a median score of 38% for the 71 patients in the present study. The increase in performance in the present study is primarily due to the higher scores of the SAS users (median score = 54%).

DISCUSSION

The results of this study clearly demonstrate that SAS is a viable speech processing option for at least one third of the patients in this study. Patients who preferred to use SAS had significantly shorter duration of deafness than patients who preferred to use CIS. The underlying cause for the relationship between duration of deafness and strategy preference is not clear. It may be that patients with shorter duration of deafness have better neural survival, allowing for greater channel independence when using a simultaneous strategy. However, the mean preoperative sentence score of the patients who preferred CIS was significantly higher than that of SAS users — a finding that also might be consistent with better nerve survival. Clearly, additional research is needed to examine the relationship between patient characteristics and strategy preference.

The study also showed that the mean word recognition score of the SAS users was significantly higher than that of the CIS users after 3 months of implant experience. These results suggest that SAS users achieve higher levels of speech recognition in a shorter period of time than do CIS users. Additional longitudinal data are needed to determine if the difference between word recognition scores of SAS and CIS users remains over time. One explanation for the higher performance of the SAS users is that the signal they receive more closely approximates that which they heard with acoustic stimulation, thereby reducing learning time. This explanation also is consistent with the shorter duration of deafness experienced by the SAS users on average.

The data also suggest that access to radically different speech processing strategies results in an increase in overall group performance. The median monosyllable word score is higher for the 71 patients implanted with the S-Series electrode compared to the performance of the patients in previous studies who had the 1.0 or 1.2 devices and were limited primarily to use of the CIS strategy. This finding is consistent with the results of another study conducted with adults implanted with the Clarion S-Series electrode. In this study, undertaken at Medizinische Hochschule Hannover in Germany, patients were fitted with CIS and SAS at the time of initial stimulation (see Battmer et al, this volume, pp 69-73). Patients then participated in a 2-week rehabilitation program, during which time they used and received an equal amount of training with each strategy. The results revealed that 10 of the 20 patients, or half of the study sample, preferred SAS, and half preferred CIS. Strategy preference was present after the 2-week rehabilitation program and did not change over time. When patients were tested with their preferred strategy, the mean score on the Freiburger monosyllable word recognition test was 39% after 3 months of Clarion use. In contrast, previous results with patients implanted with the standard electrode for whom CIS was the only viable option demonstrated a mean score of 29% after a comparable period of device use.

The present study does not permit definitive conclusions regarding the relationship between speech recognition performance and strategy preference. This study employed fitting procedures commonly used in clinical practice. Typically, the audiologist relies on the patient's subjective feedback during parameter manipulation to determine the most appropriate fitting for each patient. Thus, each patient's perceived preference for a strategy was used to determine strategy selection. The underlying assumption is that patients choose to use the processing scheme that yields the highest speech recognition performance. However, to test this assumption explicitly, patients must use each strategy for the same period of time to determine the strategy that yields the highest level of performance. A study now is under way in which experience and order of use of SAS and CIS is controlled in newly implanted adult patients with a crossover design. Speech perception performance is examined with each strategy, followed by preference testing.

Finally, simultaneous processing may become more widely applied in the future, as the variables affecting current spread and selectivity of stimulation, such as electrode placement, are better understood. As a further enhancement to the current Clarion electrode, Advanced Bionics is introducing the Electrode Positioning System (EPS), which is engineered to protect and preserve the cochlea while ensuring consistent electrode positioning close to the modiolar wall. It is anticipated that this new system will facilitate greater spatial selectivity and consequent improvements in patient performance with all of the Clarion speech processing strategies.

ACKNOWLEDGMENTS — We thank the audiologists and surgeons at the following clinical study centers for their efforts in patient enrollment, patient management, and data collection: Boys Town National Research Hospital, Omaha, Neb; House Ear Clinic, Los Angeles, Calif; Johns Hopkins University School of Medicine, Baltimore, Md; Shea Clinic, Memphis, Tenn; Tampa Bay Hearing and Balance Center, Tampa, Fla; University of California, San Francisco, Calif; University of Minnesota, Minneapolis, Minn; University of Pennsylvania, Philadelphia, Pa; and Warren Otologic Group, Warren, Ohio.

REFERENCES

1. Schindler RA, Kessler DA, Barker M. Clarion patient performance: an update on the clinical trials. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):269-72.

2. Wilson BS, Finley CC, Farmer JC Jr, et al. Comparative studies of speech processing strategies for cochlear implants. Laryngoscope 1988;98:1069-77.

3. Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. Nature 1991;35:236-8.

4. Skinner MW, Clark GM, Whitford LA, et al. Evaluation of a new spectral peak coding strategy for the Nucleus 22 channel cochlear implant system. Am J Otol 1994;15(suppl 2):15-27.

5. White MW, Merzenich MM, Gardi JN. Multichannel cochlear implants: channel interactions and processor design. Arch Otolaryngol 1984;110:493-501.

6. Loeb GE, Byers CL, Rebscher SJ, et al. Design and fabrication of an experimental cochlear prosthesis. Med Biol Eng Comput 1983;21:241-54.

7. Kessler DK. Adult patient performance with the Clarion Version 1.2. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

8. Davis H, Silverman SR. Hearing and deafness. 4th ed. New York, NY: Holt, Rinehart and Winston, 1978.

9. Cochlear Corporation and The University of Iowa Revised Cochlear Implant Test Battery. Englewood, Colo: Cochlear Corporation, 1995.

10. Lehiste I, Peterson GE. Linguistic considerations in the study of speech intelligibility. J Acoust Soc Am 1959;31:280-6.

11. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. J Speech Hear Disord 1962;27:62-70.

12. Nilsson MJ, McCaw VM, Soli S. Minimum Speech Test Battery for Adult Cochlear Implant Users. Los Angeles, Calif: House Ear Institute, 1996.

Ann Otol Rhinol Laryngol 108:1999

THE EFFECT OF LONG-TERM DEAFNESS ON SPEECH RECOGNITION IN POSTLINGUALLY DEAFENED ADULT CLARION® COCHLEAR IMPLANT USERS

LISA GEIER, MA
LAUREL FISHER, PHD
MARY BARKER, MS
JANE OPIE, PHD
SYLMAR, CALIFORNIA

Research suggests that duration of deafness prior to cochlear implantation affects postoperative speech recognition in adults. Duration of deafness usually is defined as the number of years between the onset of profound deafness and implantation. The purpose of this study was to examine the effects of duration of deafness — expressed as percentage of life with deafness — independent of age at implantation on postoperative speech recognition in adult postlingually deafened CLARION® Multi-Strategy™ Cochlear Implant users. Speech recognition tests (CID sentences and NU6 words) were administered to 202 consecutively implanted adults preoperatively and at 3 and 6 months after initial device fitting. Patients implanted at a younger age and those with smaller percentages of their lives with deafness achieved the highest levels of short-term postoperative speech recognition. Patients who had been deaf for ≥60% of their lives demonstrated a slower rate of speech recognition improvement than those with shorter durations of deafness, but still continued to improve with increased implant experience.

KEY WORDS — auditory deprivation, auditory prosthesis, cochlear implant, duration of deafness, speech recognition.

INTRODUCTION

Research has demonstrated that age at implantation and duration of deafness have significant effects on postoperative performance of postlingually deafened adult cochlear implant recipients.[1-4] Both postoperative speech recognition performance and the rate of improvement in performance over time appear to be lower and slower in persons who are deaf for a longer period of time and/or who are older when implanted. However, it is not clear from previous research what the independent contributions of duration of deafness and age at implantation are to postoperative speech recognition performance.

Duration of deafness has been defined typically as number of years with profound deafness.[3] This simple definition is useful but is limited in providing information about the potential benefit of implantation to an implant candidate. For example, different results and rates of improvement might be expected from 2 individuals with 20-year durations of deafness: 1 implanted at age 60 and 1 implanted at age 30. The older patient would have experienced auditory deprivation for one third of her life, while the younger candidate would have been deaf for two thirds of his life. Consequently, placing duration of deafness in the context of age at implantation might add relevant prognostic information, since the absolute number of years with profound deafness may not optimally reflect the extent of nerve survival, linguistic abilities, or the ability to learn to use a cochlear implant.

Two approaches have been used to assess the independent effects of duration of deafness and age at implantation on postoperative performance. Tyler and Summerfield[2] examined the correlation of postoperative performance with duration of deafness (absolute years) while controlling for age at implantation. There was a significant relationship between duration of deafness and postoperative performance. However, Tyler and Summerfield did not examine the interrelationship of duration of deafness and age at implantation to determine the relative and independent contributions of the 2 variables.

A second approach, used by Kessler et al,[5] defined duration of deafness as the percentage of one's life with deafness. This alternative definition allowed for a more direct comparison of individuals who had been deaf for an equivalent number of years, but for whom the lifetime impact of the auditory deprivation might have been different. Kessler et al found that patients who had been deaf for more than 60% of their lives performed poorer on open-set word and sentence recognition tasks than those who had been deaf for a smaller percentage of their lives. However, the study did not examine age at implantation directly, or the relationship between percentage of life with deafness and age at implantation. Nonetheless, the results indicate that duration of deafness

---

From Advanced Bionics Corporation, Sylmar, California.
CORRESPONDENCE — Lisa Geier, MA, Advanced Bionics Corporation, 12740 San Fernando Rd, Sylmar, CA 91342.

TABLE 1. REGRESSION STATISTICS FOR CID SCORE

R^2 Change Stepwise Regression

	Variable Entered	*p*
Step 1	Preop CID	.009
Step 2	Preop CID, age at implant	.013

Total Regression at Step 3

R	*df*	*F*	*p*
0.374	(3, 198)	10.72	.0001

Coefficients at Step 3

	Beta	*t*	*p*
Preop CID	0.205	3.100	.002
Age at implantation	–0.201	–3.021	.003
% of life deaf	–0.279	–4.204	.0001

TABLE 2. REGRESSION STATISTICS FOR NU6

R^2 Change Stepwise Regression

	Variable Entered	*p*
Step 1	Preop CID	.047
Step 2	Preop CID, age at implant	.004

Total Regression at Step 3

R	*df*	*F*	*p*
0.932	(3, 198)	12.017	.0001

Coefficients at Step 3

	Beta	*t*	*p*
Preop CID	0.167	2.526	.012
Age at implantation	–0.235	–3.551	.0001
% of life deaf	–0.307	–4.678	.0001

significantly affects the overall level of postimplantation speech recognition performance.

The *rate* of improvement in speech recognition performance is an issue that also may be related to duration of deafness and age at implantation. Patients achieve their maximum speech performance levels at different times after implantation. For example, Loeb and Kessler[1] reported that of the first 46 patients to receive the CLARION® Multi-Strategy™ Cochlear Implant, over half (59%) reached a plateau in speech perception performance after only 3 months of implant experience. In contrast, the other 41% of the subjects continued to show improvement at variable rates. Tyler and Summerfield[2] also demonstrated that patients had various rates of improvement in performance over time. Notably, patients who did not demonstrate benefit by 30 to 36 months after implantation tended not to show increases in scores even after 60 months of device use. Clearly, some patients show potential for benefit from an implant early on. Others require greater experience with the implant to demonstrate benefit.[6] The reasons for differential rates of postimplant performance improvements are unclear, but the rate of improvement may be related to duration of deafness.

Therefore, the purpose of this study was threefold. First, the effect of duration of deafness — expressed as percentage of life with deafness — independent of age at implantation on 6-month postoperative speech recognition performance in adult Clarion users was examined. Second, the rate of change of postoperative speech perception scores over the first year of implant use was examined as a function of the same variables. It was expected that a longer duration of deafness and an older age at implantation would result in poorer performance at 6 months after implantation and a slower rate of improvement. Third, the effect of duration of deafness — expressed as percentage of life with deafness — on rate of speech performance improvement was examined individually in patients who had been deaf for over 60% of their lives prior to receiving an implant to determine whether auditory deprivation of that magnitude consistently results in slow rates of postoperative improvement.

METHODS

Subjects. The subjects were 202 postlingually deafened adults implanted between March 1991 and August 1996 during the clinical trial of the Clarion 1.0 and 1.2 devices. Patients used either the 1.0 or 1.2 speech processor. Approximately 90% of the patients utilized the Continuous Interleaved Sampler (CIS) processing strategy, while the other 10% used the Compressed Analog (CA) strategy. Primary patient selection criteria included profound deafness bilaterally (pure tone average ≥ 90 dB hearing level), negligible hearing aid benefit (≤20% correct CID sentence score and ≤10% NU6 word score), and postlingual onset of profound deafness (onset at 6 years of age or older).

Procedures. The CID sentences and NU6 words from the Minimal Auditory Capabilities (MAC) battery were used to evaluate open-set, auditory-only speech recognition.[7] The tests were administered via tape recordings, and the stimuli were presented in free field at 63 to 68 dB sound pressure level. The subjects sat approximately 1 m from a loudspeaker at an azimuth of 45°. The patient's hearing aids or speech processor parameters (volume, sensitivity, program, etc) were set for normal conversational use. Speech recognition tests were administered to all patients preoperatively and at 3 and 6 months after initial device fitting. Some patients also were tested up to 3 years after implantation.

Data Analyses. Several different analyses were performed depending upon the experimental question. First, to examine the independent effects of per-

TABLE 3. CORRELATION OF PERFORMANCE CHANGE AND PERCENTAGE OF LIFE DEAF

		Kendall's τ	p
CID	Change preop to 3 mo	−0.173	.0001
	Change 3 mo to 12 mo	0.022	NS
NU6	Change preop to 3 mo	−0.185	.0001
	Change 3 mo to 12 mo	−0.080	NS

centage of life with deafness and age at implantation on 6-month postoperative CID and NU6 scores, the 2 variables were entered into 2 multivariate regression analyses. The predictive contribution of preoperative scores also was examined in the regression analyses. Each predictor was entered into the analysis in a stepwise fashion in that after each predictor was entered, the change in R^2 was examined to determine if more predictors could be added. Preoperative scores were entered first, followed by age at implantation and, finally, by percentage of life with deafness.

Second, the relationship between duration of deafness and rate of speech recognition improvement was examined. A correlation analysis (Kendall's τ) was used to assess the relationship between percentage of life with deafness to the changes 1) between preoperative and 3-month postoperative speech recognition scores and 2) between 3-month and 12-month postoperative speech recognition scores.

Third, to examine the rate of improvement in patients who had spent greater than 60% of their life deaf,[5] 26 individuals fitting that criteria were divided into 2 groups based upon their 3-month postoperative CID sentence scores. Patients designated "high performers" (n = 4) were those whose scores were at or above the median score for all 202 patients. Patients designated "low performers" (n = 22) were those whose scores were below the median score for all 202 patients. The rate of speech recognition improvement for the 2 groups then was examined descriptively.

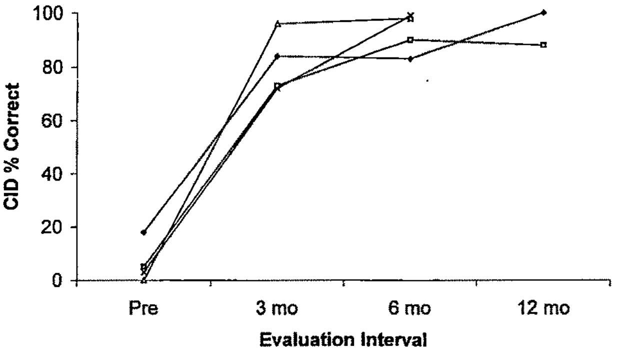


Fig 1. Individual CID sentence scores across evaluation intervals for "high performers" with ≥60% of life with deafness (n = 4).

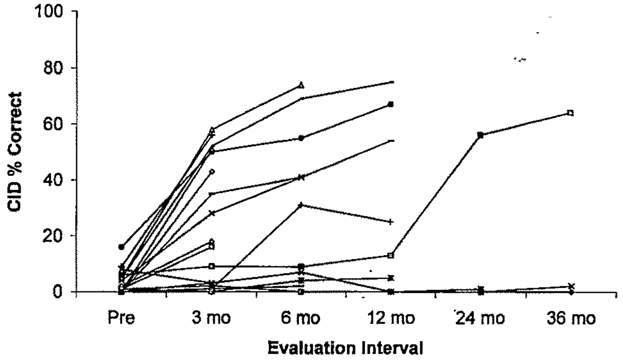


Fig 2. Individual CID sentence scores across evaluation intervals for "low performers" with ≥60% of life with deafness (n = 22).

RESULTS

Preoperative speech recognition scores, age at implantation, and percentage of life with deafness were assessed as predictors of 6-month postoperative speech recognition ability in Clarion cochlear implant recipients. As seen in Tables 1 and 2, all 3 variables significantly predicted 6-month postoperative CID and NU6 scores ($p < .05$). Higher preoperative scores, younger age at implantation, and lower percentage of life with deafness were all significantly and independently associated with higher 6-month postoperative scores.

There was a significant relationship between percentage of life with deafness and the change between preoperative and 3-month postoperative CID and NU6 scores. There was no significant relationship between percentage of life with deafness and the change between 3- and 12-month postoperative CID and NU6 scores (Table 3).

The CID sentence and NU6 word scores for the subset of patients who experienced deafness for over 60% of their lives are shown in Figs 1-4. The "high performers" achieved a plateau in performance relatively quickly (by 6 months), while the "low per-

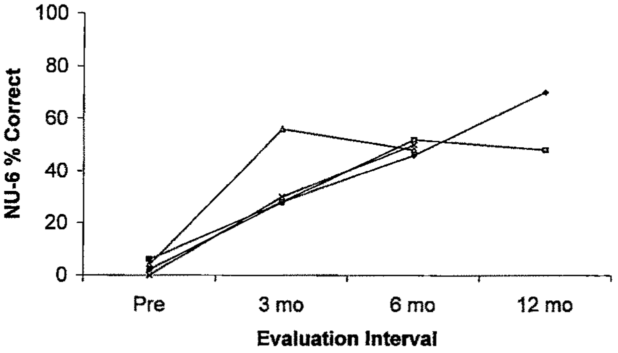


Fig 3. Individual NU6 word scores across evaluation intervals for "high performers" with ≥60% of life with deafness (n = 4).

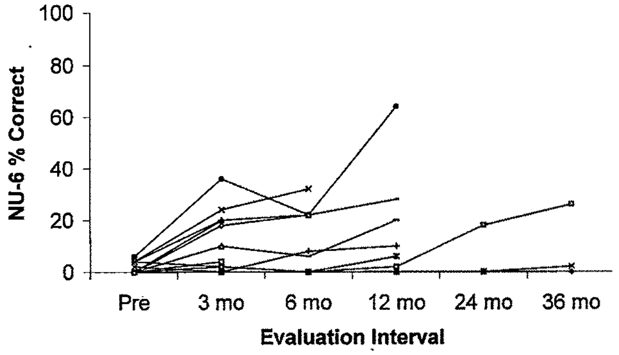


Fig 4. Individual NU6 word scores across evaluation intervals for "low performers" with ≥60% of life with deafness (n = 22).

formers" generally showed slow and variable improvement over a longer time period. The improvement in sentence scores was always greater than that in word recognition, for both groups.

DISCUSSION

This study showed that percentage of life with deafness and age at implantation have significant and independent effects on short-term postoperative performance with the Clarion cochlear implant. In addition, the results show that the rate of speech recognition improvement is dependent upon the percentage of life with deafness, at least in the first 3 months after implantation.

Thus, it appears that some implant recipients with longer proportions of their life with deafness may require more time to achieve speech recognition performance than individuals with a shorter percentage of their life with deafness. Based upon that result, it would be important clinically to counsel patients who have been deaf for a large percentage of their life that their maximum benefit may occur only after protracted implant listening experience. Moreover, the overall degree of benefit that these patients receive from an implant will be more limited than that realized by patients who are implanted after a shorter period of deafness. Thus, it is important that adult patients be implanted as soon as possible following the onset of deafness to derive the greatest benefit from a cochlear implant.

It is interesting that there was a relationship between percentage of life with deafness and the amount of change between preoperative and 3-month speech recognition scores, but no significant relationship between that variable and the amount of change in scores between 3 and 12 months after implantation. It may be that the degree of immediate postoperative improvement is dependent on factors that are directly associated with duration of deafness, for example, neural survival, experience with sound, or language ability. Speech recognition improvement that occurs later may be associated with other, as yet unexplored, factors such as learning ability, coping strategies, or rehabilitation efficacy.

It is encouraging that in spite of the strong relationship between duration of deafness and short-term speech recognition ability, the subset of patients with a large percentage of their life with deafness still experience steadily increasing improvement and benefit from their Clarion cochlear implant. For "low performer" individuals experiencing the pattern of slower change, maintaining enthusiasm and commitment to learning may be difficult, both for the clinician and the patient. Appropriate counseling of the patient and sustained encouragement by the clinician is required for these individuals to achieve maximal benefit from their device, and is a worthwhile investment of time.

ACKNOWLEDGMENTS — The authors thank the patients and clinicians who participated in the clinical trial of the Clarion cochlear implant for postlingually deafened adults.

REFERENCES

1. Loeb GE, Kessler DK. Speech recognition performance over time with the Clarion cochlear prosthesis. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):290-2.

2. Tyler RS, Summerfield AQ. Cochlear implantation: relationships with research on auditory deprivation and acclimatization. Ear Hear 1996;17(suppl 3):38-50.

3. Tyler RS, Gantz BJ, Woodworth GG, Parkinson AJ, Lowder MW, Schum LK. Initial independent results with the Clarion cochlear implant. Ear Hear 1996;17:528-36.

4. Waltzman SB, Fisher SG, Niparko JK, Cohen NL. Predictors of postoperative performance with cochlear implants. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 165):15-8.

5. Kessler DK, Loeb GE, Barker MJ. Distribution of speech recognition results with the Clarion cochlear prosthesis. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):283-5.

6. Summerfield AQ, Marshall DH. Preoperative predictors of outcomes from cochlear implantation in adults: performance and quality of life. Ann Otol Rhinol Laryngol [Suppl] 1995;104 (suppl 166):105-8.

7. Owens E, Kessler DK, Raggio MW, Schubert ED. Analysis and revision of the Minimal Auditory Capabilities (MAC) Battery. Ear Hear 1985;6:280-90.

Ann Otol Rhinol Laryngol 108:1999

IMPLANTATION OF PATIENTS WITH PRELINGUAL LONG-TERM DEAFNESS

SUSAN B. WALTZMAN, PHD NOEL L. COHEN, MD

NEW YORK, NEW YORK

The purpose of this paper is to provide performance data on long-term congenitally and prelingually deafened children and adults who are implanted with the CLARION® Multi-Strategy™ Cochlear Implant and who use the Continuous Interleaved Sampler (CIS) speech processing strategy. Open-set speech perception was assessed preoperatively and postoperatively with word and sentence recognition tests. Results indicate that a majority of subjects showed improvement from preoperative performance to the last available postoperative evaluation. These results represent a change from previously reported data on a similar population who used earlier speech processing strategies.

KEY WORDS — cochlear implant, long-term deafened, prelingual deafness.

INTRODUCTION

Improvement in open-set speech recognition skills has been well documented in congenitally and prelingually deaf children implanted at a young age.[1-5] Less information is available regarding the benefits obtained when prelingually and/or congenitally deaf children are implanted following a period of 10 years or more of profound deafness. Furthermore, based on previously published data, the prognosis for adolescents and adults with congenital and/or prelingual hearing losses attaining open-set speech recognition is considered to be poor. The majority of these reports, however, are based on results obtained with earlier speech processing technology, which may not have afforded the implant user the same access to auditory information that is currently available.

Brimacombe et al[6] reported on 24 prelingually deafened adults who received the speech feature strategy Nucleus cochlear prosthesis. Twenty-four of the subjects showed improvement in the ability to perceive prosodic features, but none of the subjects were reported to have had any open-set speech recognition. Waltzman et al[7] examined short-term results on 3 prelingually deafened adults using the Nucleus speech-feature extraction strategy. None of the subjects had measurable open-set speech recognition following 4 to 24 months of implant usage, although some improvements were seen on closed-set perceptual ability. Zwolan et al[8] found that although the prelingually deafened adults who participated in their questionnaire survey had no open-set speech recognition ability, the majority reported some level of satisfaction with their devices.

Similar results have been reported on prelingually or congenitally deaf children who received a cochlear implant following 10 years or more of deafness. Fryauf-Bertschy et al,[9] in a report on 34 prelingually deafened children, found that of the 5 children who were implanted following 10 years or more of deafness, only 1 child was a consistent device wearer. Two children were nonusers, and 2 used the implants minimally on a daily basis. Thirty-two of the children in this study used the Nucleus MPEAK strategy, while 2 children continued to use the Nucleus Wearable Speech Processor. All of the children used total communication, although some had a greater emphasis on oral communication and others used sign language as their primary mode.

The purpose of this paper is to provide specific case studies and recent general performance data on long-term congenitally or prelingually deafened children (implanted following 10 years or more of profound deafness) and adults who use the Continuous Interleaved Sampler (CIS) processing strategy as implemented in the CLARION® Multi-Strategy™ Cochlear Implant. Although 3 adults and 6 children implanted at New York University (NYU) Medical Center fit this category, follow-up data are currently available on 2 of the adults and 3 of the children. All patients use 8 active channels in a monopolar configuration and are programmed with the CIS coding strategy.

RESULTS

Subject 1. Subject 1, implanted at 20 years of age, was deafened at age 2.5 years from meningitis. The patient presented with a bilateral profound sensorineural hearing loss, was a binaural hearing aid user, and communicated orally. Preoperative unaided thresholds under earphones are shown in Table 1.

From the Department of Otolaryngology, New York University School of Medicine, New York, New York.

CORRESPONDENCE — Susan B. Waltzman, PhD, Dept of Otolaryngology, NYU School of Medicine, 550 First Ave, New York, NY 10016.

TABLE 1. PREOPERATIVE AIR CONDUCTION THRESHOLDS

Subject	*Ear*	*500 Hz*	*1,000 Hz*	*2,000 Hz*	*4,000 Hz*
1	R*	105	105	110	110
	L	95	105	110	115
2	R*	90	105	115	115
	L	90	100	105	110
3	R*	100	105	NR	NR
	L	85	105	110	NR
4	R*	95	105	120	115
	L	95	110	120	120
5	R*	95	110	NR	NR
	L	95	120	125	NR

There was no response (NR) to bone conduction stimuli.

*Ear implanted.

Open-set speech recognition scores preoperatively were 0% for words and 6% for sentences (Table 2). The patient received a Clarion cochlear implant in his right ear. During the first year following implantation, the patient had difficulty adjusting to the device and felt that perception and discrimination were better without the implant but with a hearing aid in the nonimplanted ear. At the 12-month evaluation interval, there was some improvement in open-set speech recognition compared to the preoperative level. At the third-year postoperative evaluation, however, the patient achieved scores of 26% on NU6 words and 64% on CID sentences. Furthermore, the patient reported significantly improved auditory comprehension in everyday situations and was able to conduct simple conversations on the telephone with familiar people.

Subject 2. Subject 2 was a 19-year-old bilaterally profoundly deaf adult with Waardenberg's syndrome. The hearing loss was identified at 15 months of age and was believed to be progressive in nature for a brief period prior to becoming profound. The patient used hearing aids and total communication. Preoperative unaided thresholds are shown in Table 1. The preoperative scores on the Hearing in Noise Test (HINT) sentences and Consonant Nucleus Consonant (CNC) monosyllable word test were 16% and 6%, respectively. At 3 months following implantation (last scores available), the patient achieved a score of 28% on the HINT sentence test and 12% and 30% on words and phonemes on the CNC test (Table 3). Immediately following the initial stimulation, the patient had problems adjusting to the sounds provided by the device. However, by the 3-month evaluation interval, the patient's subjective assessment regarding auditory comprehension in day-to-day conversations was very positive.

TABLE 2. PREOPERATIVE AND POSTOPERATIVE RESULTS FOR SUBJECT 1

	Preop	*3-Year Postop*
NU6 words	0%	26%
CID sentences	6%	64%

TABLE 3. PREOPERATIVE AND POSTOPERATIVE RESULTS FOR SUBJECT 2

	Preop	*3-Month Postop*
CND words	6%	12%
CNC phonemes	21%	30%
HINT sentences	16%	28%

Subject 3. Subject 3 was a 15-year-old adolescent who suffered a high fever at 9 months of age and was subsequently found to have a bilateral profound sensorineural hearing loss. The patient had used hearing aids coupled with an FM system at school since the age of 2, and used the aural-oral approach as the sole means of communication. Preoperative unaided thresholds are shown in Table 1. Because the Clarion device was under clinical trials when this patient was implanted, the required pediatric test battery was administered. Preoperatively, the patient scored 0% on Phonetically Balanced-Kindergarten (PB-K) words and 10% on the Indiana Common Phrases sentence test. At the most recent evaluation, which was 2 years postoperatively, the patient achieved a score of 16% on PB-K words and 90% on Common Phrases sentences (Table 4). The subject relies heavily on the implant and believes that it provides far more information than was obtained from hearing aids.

Subject 4. Subject 4, who was 11 years old at the time of implantation, was found to have a bilateral profound sensorineural hearing loss at 8 months of age, presumably due to ototoxic drugs administered at birth. The patient had used hearing aids and FM systems from the time of diagnosis, received communication therapy on a regular basis, and is in a mainstreamed school. The sole mode of communication is oral. Initially, the patient was reluctant to proceed with the evaluation because of fear of surgery and lack of assurance that she would hear "more and/or better" following implantation. Preoperative auditory unaided thresholds are shown in Table 1. As shown in Table 5, the following scores were obtained on open-set speech recognition tests performed preoperatively: 0% on PB-K words, 14% on PB-K phonemes, 13% on the MLNT Level 1, 24% on the LNT Level 1, and 60% on the Common Phrases sentence test. Following 1 year of implant usage,

TABLE 4. PREOPERATIVE AND POSTOPERATIVE RESULTS FOR SUBJECT 3

	Preop	*2-Year Postop*
PB-K words	0%	16%
Common Phrases	10%	90%

TABLE 5. PREOPERATIVE AND POSTOPERATIVE RESULTS FOR SUBJECT 4

	Preop	*1-Year Postop*
PB-K words	0%	52%
PB-K phonemes	14%	68%
MLNT level 1	13%	93%
MLNT level 3	DNT	93%
LNT level 1	24%	68%
LNT level 3	DNT	56%
Common Phrases sentences	60%	DNT
BKB sentences	DNT	84%

DNT — did not test.

the results were 52% on PB-K words, 68% on PB-K phonemes, 93% on the MLNT Levels 1 and 3, 68% on Level 1 and 56% on Level 3 of the LNT, and 84% on the BKB sentence test.

Subject 5. Subject 5 received a cochlear implant at 10.5 years of age. The patient presented with a bilateral profound sensorineural hearing loss, which was diagnosed at 8 months of age and believed to be congenital in nature. The child was fitted with hearing aids at 9 months of age, has been using aids since that time, and communicates using total communication. The patient is mainstreamed with a full-time interpreter and receives speech therapy several times a week. Preoperative unaided thresholds are shown in Table 1. Preoperative and 3-month postoperative scores on speech perception tests are shown in Table 6. Although minimal improvements are shown on formal tests, there appears to be a trend toward improved scores on the majority of word and sentence tests. Both the patient and family report increased and improved understanding of speech in school and at home.

TABLE 6. PREOPERATIVE AND POSTOPERATIVE RESULTS FOR SUBJECT 5

	Preop	*3-Month Postop*
PB-K words	0%	0%
PB-K phonemes	14%	19%
MLNT words	4%	13%
MLNT phonemes	15%	18%
LNT words	0%	12%
LNT phonemes	12%	16%
Common Phrases	20%	10%
BKB sentences	2%	10%

DISCUSSION

The data reveal a trend toward acquisition of open-set speech recognition in long-term–deafened children and adults using the CIS processing strategy as implemented in the Clarion multistrategy cochlear prosthesis. All 5 patients described here improved in their ability to understand words and/or sentences following implantation with the Clarion device. (These results are in agreement with those of Osberger et al,[10] who have reported 3- and 6-month postoperative data from congenitally or prelingually profoundly deaf older children and adolescents who were implanted above 10 years of age.) By inspection, these results indicate a more favorable prognosis compared to previously published reports of subjects with similar baseline characteristics who used a feature-extraction speech processing strategy. Although definitive results from patients using the Nucleus CI24M cochlear implant are not yet available, a review of early data obtained from 3 similar adults implanted with the CI24M at NYU Medical Center reveals similar trends in the development and improvement of open-set word and sentence recognition. In a previously published study of adults using either the Nucleus F0-F2 or F0-F1-F2 processing scheme, subjects who did not possess speech recognition abilities within a short time following stimulation did not develop these skills over time.[11] In contrast, subject 1, who used the Clarion implant, developed the ability to understand words and sentences over a period of 3 years following implantation. One might postulate that other implanted patients programmed with more recent processing strategies who initially exhibit minimal or no speech discrimination ability might develop better auditory skills over time.

Of the 22 older children (including 2 of the subjects implanted at NYU Medical Center) for whom Advanced Bionics has data, 12 are oral communicators, 8 use total communication, and 2 use cued speech. Three-month postoperative data are available for 21 children. It is interesting to note, although too soon to draw conclusions, that of the 15 children who exhibit some open-set word or sentence perception at the 3-month interval, 10 are oral communicators, 3 use total communication, and the remaining 2 children use cued speech. The highest perception scores, however, are found in those subjects who use oral speech and language as their sole mode of communication. It will be interesting to observe if this trend continues over time.

Baseline demographics also may contribute to the improved performance currently observed in the long-term–deafened population who use the CIS strategy. Criteria for implantation in the late 1980s and early 1990s were more restrictive in nature. Depending on the specific device protocol or clinical trial, pure tone thresholds of prospective candidates were frequently worse than are currently acceptable, and subjects often were not permitted to demonstrate any measurable open-set word or sentence recognition preoperatively. Since recent preliminary studies have shown some correlation between preoperative hearing levels and perception scores and postoperative performance, the relationship between these preoperative variables, the speech coding strategy, and improved postoperative scores should be explored further.[12-14]

CONCLUSIONS

Congenitally and prelingually deafened adults — and congenitally and prelingually long-term–deafened children — can develop auditory recognition skills using current technologically advanced cochlear prostheses. The extent to which the advantages of recent cochlear implants reflect less restrictive criteria for implantation, baseline auditory and/or demographic differences, and method of communication or other associated factors has yet to be determined.

REFERENCES

1. Fryauf-Bertschy H, Tyler R, Kelsay D, Gantz B. Performance over time of congenitally deaf and postlingually deafened children using a multichannel cochlear implant. J Speech Hear Res 1992;35:913-20.

2. Gantz B, Tyler R, Woodworth G, Tye-Murray N, Fryauf-Bertschy H. Results of multichannel cochlear implants in congenital and acquired prelingual deafness in children: five-year follow-up. Am J Otol 1994;15(suppl 2):1-7.

3. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl 2):9-13.

4. Waltzman SB, Cohen NL, Gomolin RH, et al. Open-set speech perception in congenitally deaf children using cochlear implants. Am J Otol 1997;18:342-9.

5. Waltzman SB, Cohen NL. Cochlear implantation in children younger than two years old. Am J Otol 1998;19:158-62.

6. Brimacombe J, Beiter A, Barker M, et al. Cochlear implant results in pre-perilinguistically deafened adults. Presented at the 92nd Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery, New Orleans, Louisiana, Sept 24-8, 1989.

7. Waltzman S, Cohen N, Shapiro W. Use of a multichannel cochlear implant in the congenitally and prelingually deaf population. Laryngoscope 1992;102:395-9.

8. Zwolan T, Kileny P, Telian S. Self-report of cochlear implant use and satisfaction by prelingually deafened adults. Ear Hear 1996;17:199-210.

9. Fryauf-Bertschy H, Tyler R, Kelsay D, Gantz B, Woodworth G. Cochlear implant use by prelingually deafened children: the influences of age at implant and length of device use. J Speech Lang Hear Res 1997;40:183-99.

10. Osberger MJ, Fisher L, Zimmerman-Phillips S, Geier L, Barker M. Speech recognition performance of older children with cochlear implants. Am J Otol 1998;19:152-7.

11. Spivak L, Waltzman S. Performance of cochlear implant patients as a function of time. J Speech Hear Res 1990;33:511-9.

12. Fisher L, Osberger MJ. Relationship between pre- and post-implant speech perception skills in pediatric Clarion patients. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

13. Seghal S, Kirk K, Pisoni D, Miyamoto R. Effect of residual hearing on children's speech perception abilities with a cochlear implant. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

14. Cowan R, Dettman S, Pegg P, Barker J. Preoperative residual hearing as an indicator of postoperative benefit from multichannel cochlear implants. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

Ann Otol Rhinol Laryngol 108:1999

CLINICAL TRIAL OF THE CLARION® COCHLEAR IMPLANT IN CHILDREN

MARY JOE OSBERGER, PHD
SUSAN ZIMMERMAN-PHILLIPS, MS
MARY BARKER, MS
LISA GEIER, MA
SYLMAR, CALIFORNIA

Preoperative and postoperative efficacy results are reported for the first 58 children with 18 months of implant experience in the United States. A within-subjects repeated-measures design was used to compare preoperative performance with hearing aids to postoperative performance with the CLARION® Multi-Strategy™ Cochlear Implant. The results revealed significant improvement over time on all speech perception measures. Higher scores and faster rates of progress were demonstrated by the children who used oral communication compared to children who used total communication, especially older children. The overall results suggest higher levels of performance and more rapid progress in the development of listening skills than has been reported in previous clinical trials with children. The latter finding appears to be due to advances in implant technology and changes in the demographic characteristics of the study groups.

KEY WORDS — children, cochlear implant, communication mode.

INTRODUCTION

The clinical trial of the CLARION® Multi-Strategy™ Cochlear Implant in children was initiated in March 1995 and concluded in June 1997, when the US Food and Drug Administration released the device for commercial distribution in the pediatric population. At the time of the approval, 256 children in the United States and 278 children in foreign countries had been implanted with the Clarion. Data from the first 73 children with 6-month postoperative results in the US study group were used to establish the effectiveness of the Clarion. A postmarket surveillance study has been ongoing to monitor the long-term effectiveness of the Clarion in the same 73 children. To date, 58 of the 73 children have been evaluated through 18 months of implant use. This report summarizes the longitudinal performance of these 58 children on a battery of speech perception tests.

Previous pediatric results with the Clarion, as well as findings reported with other devices, have shown a wide range in performance among implanted children.[1-4] One variable that has been shown to have a significant effect on postimplant performance is preoperative communication mode.[5-7] Therefore, data in this study were analyzed as a function of this variable.

METHODS

Subjects. Children were enrolled in the clinical trial if they met the following inclusion criteria: 2 to 17 years of age, profound bilateral hearing loss, no functional benefit from hearing aids, minimum of 6 months elapsed since the onset of deafness, hearing aid trial of at least 6 months, no evidence of mental retardation, and English as the primary language. All of the children were classified as prelingually deafened (ie, onset of deafness before age 2). They also showed no functional hearing aid benefit, which was defined as a score of 0% on the Phonetically Balanced-Kindergarten (PB-K) word identification test. If the PB-K test was developmentally inappropriate, negligible hearing aid benefit was defined as a score of ≤2 on questions 3 (response to name), 5 (response to environmental sounds), and 6 (shows curiosity about new sounds) on the Meaningful Auditory Integration Scale (MAIS).[8]

The demographic characteristics of the children are summarized in Table 1 as a function of preoperative communication mode and test level (Level 1 or Level 2, described below). Oral children were those children who communicated using audition, speechreading, and speech. Total communication (TC) children employed an English-based sign system as well as audition, speechreading, and speech.

Evaluation Materials. Children were evaluated on

TABLE 1. BACKGROUND CHARACTERISTICS OF CHILDREN ADMINISTERED LEVEL 1 AND LEVEL 2 TESTS BY COMMUNICATION MODE

	Level 1		*Level 2*	
	Oral (n = 24)	*TC (n = 12)*	*Oral (n = 17)*	*TC (n = 5)*
Mean age at implantation (y)	3.6	3.1	8.5	9.0
Mean age at onset of deafness (y)	0.4	0.5	1.8	0.7
Mean unaided pure tone average (dB hearing level)	108	116	107	111

TC — total communication.

From Advanced Bionics Corporation, Sylmar, California.

CORRESPONDENCE — Mary Joe Osberger, PhD, Advanced Bionics Corporation, 12740 San Fernando Rd, Sylmar, CA 91342.

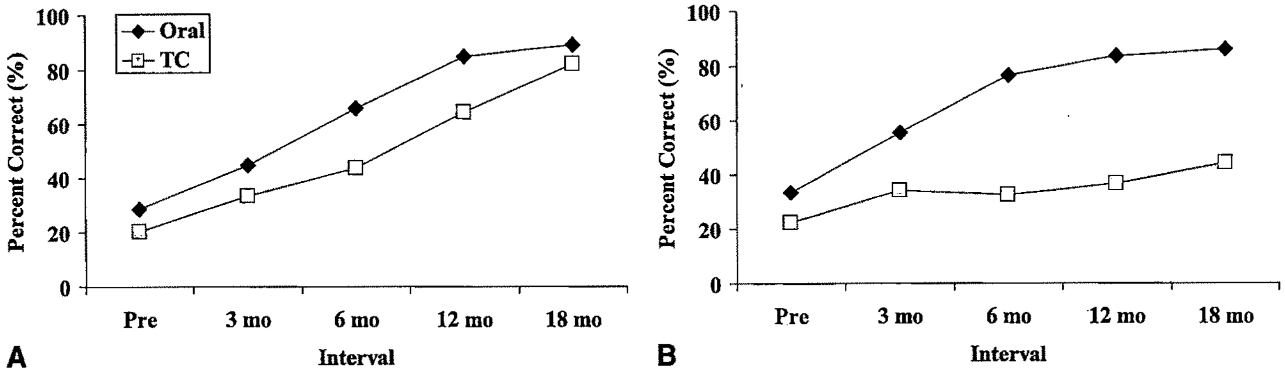


Fig 1. Mean preoperative and postoperative scores (percent correct) on closed-set ESP Monosyllable Word Identification test for A) younger children implanted with Clarion (mean age at implantation = 3.4 years) and B) older children implanted with Clarion (mean age at implantation = 8.8 years) as function of communication mode.

a battery of speech perception measures to determine the effectiveness of the Clarion. Two levels of test difficulty were employed, depending upon age and perception ability. Level 1 tests were administered to all children less than 4 years of age. Level 2 tests were administered to all children 7 years of age and older. Children 4, 5, or 6 years old were administered a screening test to assess basic vocabulary skills and to determine if Level 1 or Level 2 tests were more appropriate.

Closed-set word identification was assessed with the Monosyllable Word Identification subtest of the Early Speech Perception (ESP) test.[9] The Low Verbal version, consisting of 4 objects (3 repetitions of each of the 4 items; chance = 25%), was used for Level 1 testing. The Standard version, consisting of 12 pictured words (2 repetitions of each word; chance = 8%) was used for Level 2 testing.

Open-set word identification was evaluated with the Glendonald Auditory Screening Procedure (GASP).[10] It consists of 12 words of different syllable numbers and/or stress patterns (chance = 0%). The child repeats the word that is presented by the examiner. This test was administered to all children.

For Level 1 children, the Mr Potato Head Task[11] was used to assess recognition of key words and simple commands. It uses the Mr Potato Head toy and the 24 parts that accompany it (eg, "Put a *hat* on Mr Potato Head"). Performance is scored as the percentage of key phrases (n = 10) that are correctly identified. Because there are a large number of response alternatives (ie, 24, with chance performance = 4%), this test typically is considered to be an open-set test for young children with limited linguistic skills and test-taking strategies.

For Level 2 children, the Common Phrases test[12] was used to assess understanding of familiar phrases encountered in everyday situations. Performance is scored as the percentage of complete phrases (n = 10) that are correctly identified (chance = 0%).

For both Level 1 and Level 2, the PB-K test[13] was used to evaluate open-set word recognition. It consists of 50 phonetically balanced words that are within the vocabularies of 5-year-old normal-hearing children. Half-lists of 25 words were used and scores indicate both the number of phonemes (n = 70 in each half-list) and words (n = 25) correctly identified (chance = 0%).

Procedures. All speech perception measures were administered via listening alone (ie, without speechreading) by means of live-voice presentation. The tests were administered preoperatively while the children were using hearing aids and postoperatively at 3, 6, 12, and 18 months while they were using their Clarion implants. All children used the Continuous Interleaved Sampler (CIS) strategy in their Clarion speech processors.

Raw scores were converted to percent correct on each test. Children were assigned a score of chance on the tests if they were unable to understand the instructions and/or the test was determined by the audiologist to be developmentally inappropriate. Data were subjected to repeated-measures analysis of variance with test level (Level 1 and Level 2) and communication mode (oral and TC) as between-subjects variables and time (preimplantation and at 3, 6, 12, and 18 months) as a within-subjects variable. For the PB-K test, which consisted of 2 scores (phoneme and word), a double repeated-measures analysis was performed with both evaluation interval and score as repeated variables.

RESULTS

Preoperative and postoperative performance on the speech perception tests is summarized by test level and communication mode in Figs 1-4. The results of the analyses revealed a significant effect of time ($p < .0001$) on all measures. That is, there was a statisti-

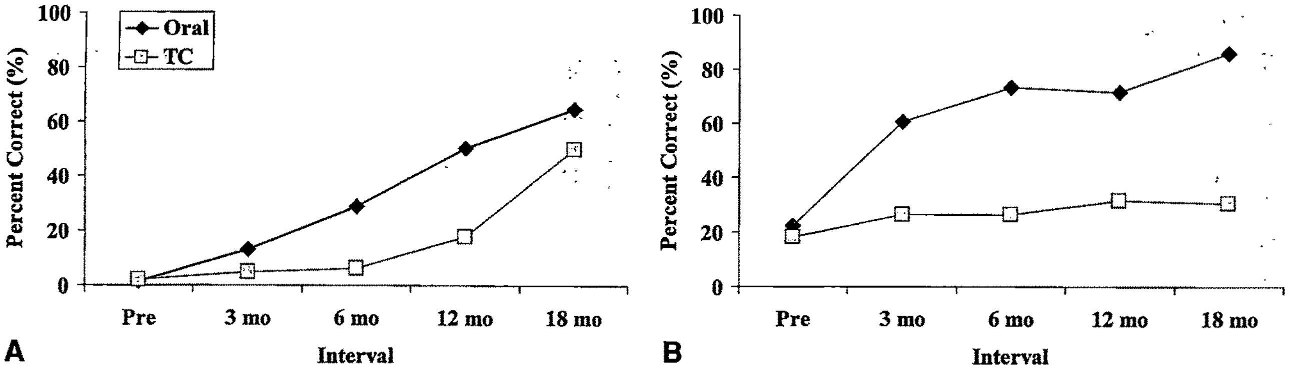


Fig 2. Mean preoperative and postoperative scores (percent correct) on open-set GASP word test for A) younger children implanted with Clarion (mean age at implantation = 3.4 years) and B) older children implanted with Clarion (mean age at implantation = 8.8 years) as function of communication mode.

cally significant improvement in performance over time on all measures by all children (Level 1 and Level 2).

Performance on the ESP Monosyllable Word Identification test is shown in Fig 1A and Fig 1B for Level 1 and Level 2 children, respectively. The scores of the oral children were significantly higher than those of the TC children (F(1,52) = 14.9; p < .0001). The main effect of test level was not significant, indicating no difference between the performance of the children tested with the Level 1 and Level 2 protocols. There was, however, a significant interaction between time and test level (F(4,208) = 3.52; p < .01), as well as a significant interaction between time and communication mode (F(4,208) = 3.26; p < .01). These interactions suggest that performance increased most rapidly for the children who used oral communication and for the younger children. Note the similarity in performance over time between the Level 1 oral and TC children. In contrast, there is a large difference between the scores of the older (Level 2) children who used oral communication and TC at all intervals. Overall, the mean scores suggest that the test ceiling on the ESP is reached after about 6 months of implant use in the Level 2 oral children and after approximately 12 months of use for all of the Level 1 children.

Figure 2 shows the GASP word scores as a function of test level and communication mode. Again, the scores of the oral children were significantly higher than those of the TC children (F(1,33) = 13.5; p < .001), but there was no significant difference between the scores of the younger (Level 1) and older (Level 2) children. There also was a significant time-by-communication mode interaction (F(4,132) = 2.4; p < .05), indicating faster progress by the oral than the TC children. After 6 months of device use, the mean scores of the older (Level 2) children are relatively high and appear to be approaching the test ceiling. In contrast, the scores of the TC children show negligible improvement over time (Fig 2B). For the younger children, improvement on the GASP was not obvious in the TC children until after 12 months of implant use, with negligible difference between the oral and TC children at the 18-month interval (Fig 2A).

Figure 3A summarizes performance on the Mr Potato Head Task for the Level 1 children. On this measure, there was no significant difference between the performance of the oral and TC children. Note that the mean score for each group remains close to 0%

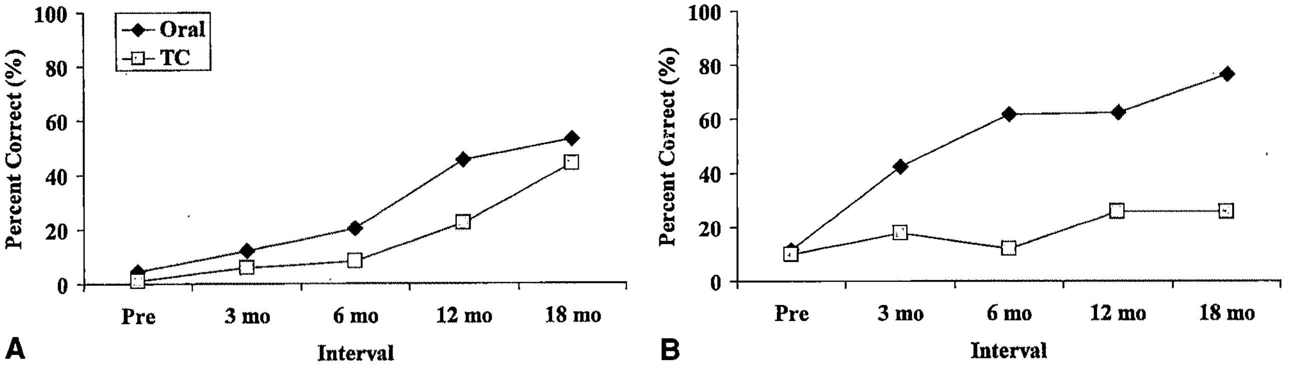


Fig 3. Mean preoperative and postoperative sentence scores (percent correct) on A) open-set Mr Potato Head Task for younger children implanted with Clarion (mean age at implantation = 3.4 years) and B) open-set Common Phrases test for older children implanted with Clarion (mean age at implantation = 8.8 years) as function of communication mode.

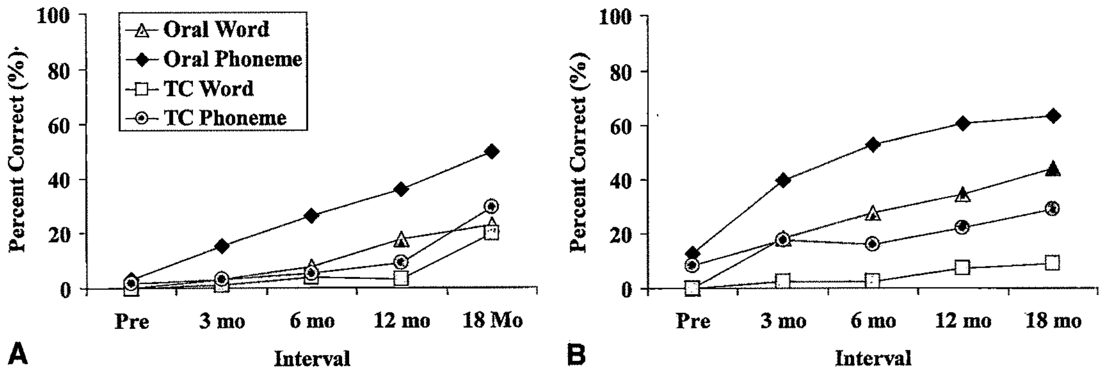


Fig 4. Mean preoperative and postoperative phoneme and word scores (percent correct) on open-set PB-K test for A) younger children implanted with Clarion (mean age at implantation = 3.4 years) and B) older children implanted with Clarion (mean age at implantation = 8.8 years) as function of communication mode.

until the 12-month interval, with improvement after 18 months of implant use.

Figure 3B shows the performance of the older (Level 2) children on the Common Phrases test. There was a significant effect of communication mode ($F(1,19) = 5.6$; $p < .05$) and a significant interaction between time and communication mode ($F(4,76) = 4.17$; $p < .01$), indicating higher scores and a faster learning rate for the oral compared to the TC children. There is negligible improvement in the performance of the TC children, compared to a rapid increase in the scores of the oral children.

Figure 4 shows the results for the PB-K tests for phonemes and words. For PB-K phonemes, there was a significant effect of communication mode ($F(1,52) = 14.1$; $p < .0001$) and test level ($F(1,52) = 8.7$; $p < .01$), indicating that scores of the oral children and Level 2 children were higher than those of the TC children or Level 1 children. The higher performance of the older children is not surprising, given that the vocabulary on this test was probably above the language skills of most of the younger children. There also was a significant interaction between time and communication mode ($F(4,208) = 5.35$; $p < .0001$), indicating that faster progress was made by the oral than the TC children.

Similar findings occurred for the PB-K words. There was a significant effect of communication mode ($F(1,52) = 9.5$; $p < .01$) but no significant test level effect, indicating that the task was difficult for both younger and older children. The rate of progress was faster for oral than TC children, shown by the significant interaction between time and communication mode ($F(208) = 4.1$; $p < .01$).

Tables 2 and 3 illustrate the variance in performance that occurred at the 18-month interval. On many of the measures, the median score is higher than the mean, reflecting the non-normal distribution of the scores. For example, on the GASP test, the mean score for the oral children was 63% but the median was 75%, indicating that half of the children scored 75% or higher on this measure after 18 months of implant use. The sizes of the standard deviations indicate substantial variance in performance among the children even when they are of the same developmental level or use the same mode of communication.

DISCUSSION

The results of this study are in agreement with those of previous investigations in that children who use oral communication show higher performance than children who use TC.[5-7] In this study, the difference between the scores of the oral and TC children was most obvious for the older children (ie, Level 2). In fact, the older children who used TC made negligible improvement on most of the measures, presumably because they experienced many years of auditory deprivation prior to implantation. It should be noted that only 5 of the 22 Level 2 children used TC. This observation suggests that fewer older children with limited auditory potential seek a

TABLE 2. SCORES (PERCENT) ON SPEECH PERCEPTION TESTS FOR PEDIATRIC PATIENTS ADMINISTERED LEVEL 1 TESTS AFTER 18 MONTHS OF CLARION USE

	Oral Communication			*Total Communication*		
	Mean	*SD*	*Median*	*Mean*	*SD*	*Median*
Monosyllable Word	90	22	100	82	29	100
GASP word	63	37	75	50	39	54
Mr Potato Head	54	35	55	44	36	45
PB-K phoneme	50	27	61	29	34	11
PB-K word	24	19	24	20	27	2

TABLE 3. SCORES (PERCENT) ON SPEECH PERCEPTION TESTS FOR PEDIATRIC PATIENTS ADMINISTERED LEVEL 2 TESTS AFTER 18 MONTHS OF CLARION USE

	Oral Communication			*Total Communication*		
	Mean	*SD*	*Median*	*Mean*	*SD*	*Median*
Monosyllable Word	86	17	96	44	32	42
GASP word	86	19	92	31	27	42
Common Phrases	76	34	90	26	37	20
PB-K phoneme	61	26	64	29	27	27
PB-K word	79	32	95	9	18	0

cochlear implant relative to older children who use oral communication. Nonetheless, clinical report indicates that these children still derive benefits from their implants, such as enhanced speechreading performance, that were not tapped by the assessment procedures in this study.

In contrast, there was a smaller performance difference between the younger (Level 1) children as a function of communication mode. Presumably, if TC children are implanted at a young age, they become more like auditory-oral communicators as they develop auditory perception and speech production skills with their cochlear implants. In fact, the preferred mode of communication may change over time as oral communication skills improve in TC children. In this study, communication mode was assessed only in the preimplant condition, but longitudinal follow-up will be able to identify changes in communication mode that occur with prolonged implant use.

The results of the study also are consistent with previous investigations in that performance improves over an extended time course.[1-4] However, the rate of learning appears to be faster in this group of children than reported in previous studies. This difference presumably reflects changes in the demographic characteristics of the study groups, as well as advances in implant technology. Results obtained with the Clarion suggest that the ESP Monosyllable Word test ceiling is reached after relatively limited device experience (6 to 12 months). Moreover, there was evidence of open-set speech recognition skills after only 3 to 6 months of device use. Continued improvement in performance is anticipated with more extended implant experience, especially in the younger children as they acquire language and test-taking skills.

In summary, the results of this study continue to suggest that communication mode and developmental level are 2 factors that contribute to the variance in speech perception performance in implanted children. Notably, a previous study on the same children revealed that preoperative speech perception skills also were a significant predictor of postimplant performance.[14] Additional research is needed to identify other variables that account for the range in benefit demonstrated by children who receive cochlear implants.

ACKNOWLEDGMENTS — We thank the surgeons and audiologists at the 25 investigational centers in the clinical trial for their efforts in patient enrollment, patient management, and data collection.

REFERENCES

1. Osberger MJ, Miyamoto RT, Zimmerman-Phillips S, et al. Independent evaluation of the speech perception abilities of children with the Nucleus 22-channel cochlear implant system. Ear Hear 1991;12(suppl):66S-80S.
2. Staller SJ, Beiter A, Brimacombe J, Mecklenburg D, Arndt P. Pediatric performance with the Nucleus 22-channel cochlear implant system. Am J Otol 1991;12(suppl):126-36.
3. Fryauf-Bertschy H, Tyler RS, Kelsay DM, Gantz BJ, Woodworth GG. Cochlear implant use by prelingually deafened children: the influences of age at implant and length of device use. J Speech Hear Res 1997;40:183-99.
4. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl 2):9-13.
5. Somers MN. Speech perception abilities in children with cochlear implants or hearing aids. Am J Otol 1991;12(suppl): 174-8.
6. Quittner A, Steck J. Predictors of cochlear implant use in children. Am J Otol 1991;12(suppl):89-94.
7. Osberger MJ, Zimmerman-Phillips S, Fisher L. Relationship between communication mode and implant performance in pediatric CLARION patients. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.
8. Robbins AM, Renshaw JJ, Berry SW. Evaluating meaningful auditory integration in profoundly hearing-impaired children. Am J Otol 1991;12(suppl):144-50.
9. Moog JS, Geers AE. Early speech perception test. St Louis, Mo: Central Institute for the Deaf, 1990.
10. Erber NP. Auditory training. Washington, DC: Alexander Graham Bell Association, 1982.
11. Robbins AM. Mr Potato Head Task. Indianapolis, Ind: Indiana University School of Medicine, 1993.
12. Robbins AM, Renshaw JJ, Osberger MJ. Common Phrases Test. Indianapolis, Ind: Indiana University School of Medicine, 1988.
13. Haskins H. A phonetically balanced test of speech discrimination for children [Thesis]. Evanston, Ill: Northwestern University, 1949.
14. Osberger MJ, Fisher L. Preoperative predictors of postoperative implant performance in children. Presented at the 7th Symposium on Cochlear Implants in Children, Iowa City, Iowa, June 4-7, 1998.

Ann Otol Rhinol Laryngol 108:1999

SPEECH PERCEPTION RESULTS FOR CHILDREN IMPLANTED WITH THE CLARION® COCHLEAR IMPLANT AT THE MEDICAL UNIVERSITY OF HANNOVER

ANGELIKA ILLG
HANNOVER, GERMANY
SABINE VON DER HAAR-HEISE
HANNOVER, GERMANY
JENNY E. GOLDRING, MSC
MERZIG, GERMANY
ANKA LESINSKI-SCHIEDAT, MD
HANNOVER, GERMANY
ROLF D. BATTMER, PHD
HANNOVER, GERMANY
THOMAS LENARZ, MD, PHD
HANNOVER, GERMANY

The perception of speech of 167 children implanted with a CLARION® Multi-Strategy™ Cochlear Implant (1.2 device) was evaluated preimplantation and at 3, 6, 12, 18, and 24 months postimplantation. The children were between 15 months and 15 years of age. The test materials consisted of 8 tests involving syllable structure, single- and 2-syllable words, differentiation of word pairs, and sentences. Two difficulty levels were used, depending on developmental age (<7, and 7 to 15 years). There was an improvement in test scores over time for both age groups. The younger children (particularly those under age 4) improved steadily over the first 2 years, while the older children tended to plateau between 12 and 18 months after implantation. These findings demonstrate that deaf children up to 15 years old benefit from cochlear implants. Children under 4 years of age may even have the ability to compensate for delays in speech development before they reach school age.

KEY WORDS — children, cochlear implant, speech perception.

INTRODUCTION

Over the last decade, cochlear implants have been used increasingly for patients with bilateral deafness.[1] The success experienced by postlingually deafened adults with cochlear implants led to the implantation of prelingually deafened children. The main goal for children is improved hearing and speech development, which may allow integration into mainstream schools. The Medical University of Hannover (Medizinische Hochschule Hannover; MHH) began implanting the CLARION® Multi-Strategy™ Cochlear Implant in children in 1994. Since that time, hearing and speech perception and production development, before and after implantation, have been evaluated regularly. This paper presents the test results for the Clarion children at MHH, investigating the effect of age at implantation on performance.

METHODS

Between 1994 and 1997, 167 children ranging in age from 15 months to 15 years (average 6.5 years) were implanted with a Clarion cochlear implant.[2] All are presently using the 1.2 speech processor and are programmed with the Continuous Interleaved Sampler (CIS) strategy. Children implanted in 1994 and early 1995 received a 1.0 speech processor, which was upgraded to a 1.2 speech processor between the fall of 1995 and winter of 1996. Almost all of the children were deafened before learning oral speech and language. (Fewer than 10 were postlingually deafened.) The cause of deafness was most commonly meningitis or congenital.

The hearing and speech test battery was developed to be similar to that used in the Clarion children's clinical trial, but was modified for the German language.[3] The test battery consisted of 8 subtests to evaluate various speech and language skills. Test material included 2 difficulty levels: level 1 for the children under age 7, and level 2 for the children between 7 and 15 years. Developmental age was used to determine the group. Results are presented for these 2 groups. To further investigate the effect of age at implantation on performance, the level 1 group was divided into 2 age groups: <4 years (n = 66, average age = 2.7 years) and 4 to 7 (n = 37, average age = 5.5 years). Tests were administered preoperatively and at 3, 6, 12, 18, and 24 months after implantation (although the number of children tested was less at the later test periods; Tables 1 and 2). Both open- and closed-set test conditions were used. In the closed-set conditions, the therapist said a word, and the child had to point to a picture. In the open-set conditions, the child had to repeat the words spoken by the therapist. The following subtests were administered.

Closed-Set Tests. The closed-set tests were as follows.

From the Department of Otolaryngology, Medizinische Hochschule Hannover, Hannover, and Advanced Bionics GmbH, Merzig (Goldring), Germany.

CORRESPONDENCE — Angelika Illg, Dept of Otolaryngology, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.

TABLE 1. CLOSED-SET TEST RESULTS FOR LEVEL 1 AND LEVEL 2

	Preop	*3-Month*	*6-Month*	*12-Month*	*18-Month*	*24-Month*
Level 1 closed-set						
Pattern Perception						
Scores (%)	27	40	46	65	71	86
SD (%)	11	29	31	33	30	24
N	109	82	57	39	23	10
Two-syllable test						
Scores (%)	27	39	45	59	74	81
SD (%)	11	26	30	33	30	25
N	109	82	57	39	23	10
Monosyllable test						
Scores (%)	27	38	47	66	72	78
SD (%)	11	25	30	32	32	30
N	109	82	57	39	23	10
Minimal Pairs						
Scores (%)	50	51	52	53	57	60
SD (%)	2	7	8	8	15	15
N	109	82	57	38	22	10
Level 2 closed-set						
Pattern Perception						
Scores (%)	31	61	72	75	70	70
SD (%)	32	28	24	25	29	28
N	58	41	45	34	18	11
Two-syllable test						
Scores (%)	22	35	48	52	55	47
SD (%)	23	27	31	31	33	35
N	58	41	45	33	18	11
Monosyllable test						
Scores (%)	21	35	51	57	58	56
SD (%)	22	25	30	32	34	31
N	58	41	45	33	18	11
Minimal Pairs						
Scores (%)	50	56	62	64	67	65
SD (%)	9	12	13	11	12	10
N	58	41	45	33	17	10

1. Pattern Perception. The child had to recognize patterns of syllables (an easy task).

2. Two-Syllable Word Test. The child had to recognize familiar 2-syllable words.

3. Monosyllable Word Test. The child had to recognize monosyllabic words.

4. Minimal Pairs Test. The child had to find the picture corresponding to 1 of 2 similar words.

Open-Set Tests. The open-set tests were as follows.

1. TAPS Word Test (Test of Auditory Perception and Speech). The child had to repeat 12 words, each with a different number of syllables. This test is comparable to the Glendonald Auditory Screening Procedure (GASP)[4] word identification task.

2. Monosyllable Word Test. Twenty monosyllabic words had to repeated by the child. This test is comparable to the Phonetically Balanced-Kindergarten (PB-K) word test.[5]

3. GASP Sentence Test. The child had to answer questions appropriately.[4]

4. Common Phrases. Ten sentences had to be repeated by the children in the level 2 group. For the younger children (level 1), the Mr Potato Head Task was used. This test requires the child to manipulate a toy and associated objects when asked various questions.[6]

RESULTS

Closed-Set Tests. The results for the 4 closed-set tests are displayed in Fig 1. Actual scores with standard deviations and number of subjects are listed in Table 1. In general, the results were very good for both groups, although the improvement as a func-

TABLE 2. OPEN-SET TEST RESULTS FOR LEVEL 1 AND LEVEL 2

	Preop	*3-Month*	*6-Month*	*12-Month*	*18-Month*	*24-Month*
Level 1 open-set						
TAPS test						
Scores (%)	1	11	18	34	45	57
SD (%)	7	28	31	37	36	29
N	109	82	57	39	23	10
Monosyllable test						
Scores (%)	1	10	15	30	39	55
SD (%)	6	25	27	33	33	30
N	109	82	57	39	23	10
GASP test						
Scores (%)	1	1	1	3	6	9
SD (%)	6	5	4	6	15	14
N	109	82	57	39	23	9
Mr Potato Head Task						
Scores (%)	0	3	3	14	16	22
SD (%)	3	10	12	24	25	31
N	107	78	54	37	22	9
Level 2 open-set						
TAPS test						
Scores (%)	7	24	41	49	45	44
SD (%)	19	29	34	36	35	36
N	58	41	45	33	18	10
Monosyllable test						
Scores (%)	5	17	33	38	40	41
SD (%)	17	22	29	29	30	33
N	58	41	45	32	18	10
GASP test						
Scores (%)	2	9	22	23	20	25
SD (%)	14	20	33	31	26	27
N	58	41	45	34	18	10
Common phrases						
Scores (%)	3	6	13	17	11	17
SD (%)	12	15	25	31	22	23
N	57	40	44	32	18	10

tion of time differed between the younger and older children. Preoperatively, the level 1 children attained only a chance level score (25%). After implantation, they showed a steep improvement for the Pattern Perception (PP), 2-syllable word, and monosyllable word tests over the 2-year testing period. The results for the 3 tests were similar in that the scores improved steadily to about 80% to 85% by 2 years postimplantation.

In contrast to the level 1 children, the level 2 children started with better-than-chance level scores (chance score was 8%). This preimplant difference can be attributed to longer hearing aid and language experience. The scores for the first 3 closed-set tests for the level 2 children also steadily improved in the first year, but seemed to begin to plateau by 12 to 18 months after implantation (about 75%, 52%, and 57% at 12 months for the PP, 2-syllable, and monosyllable word tests, respectively). In fact, there was no significant difference between the 12-, 18-, and 24-month scores for the level 2 children (Wilcoxon, $p < .05$). When the level 1 and 2 scores are compared at 1.5 to 2 years, the younger children have better scores on average (although the total number of children who reached the full 2-year testing session was quite low). The Minimal Pairs test was more difficult, and the improvement for both age groups was smaller. For this test, both groups had preoperative scores at the chance level (50%), improving over time to 60% and 65% for level 1 and 2 children, respectively.

When the level 1 results are broken down into ages <4 and 4-to-7, it is evident that the youngest children show a very steep improvement curve on the PP, 2-syllable, and monosyllable tests, which presumably will continue to rise past 24 months (Fig

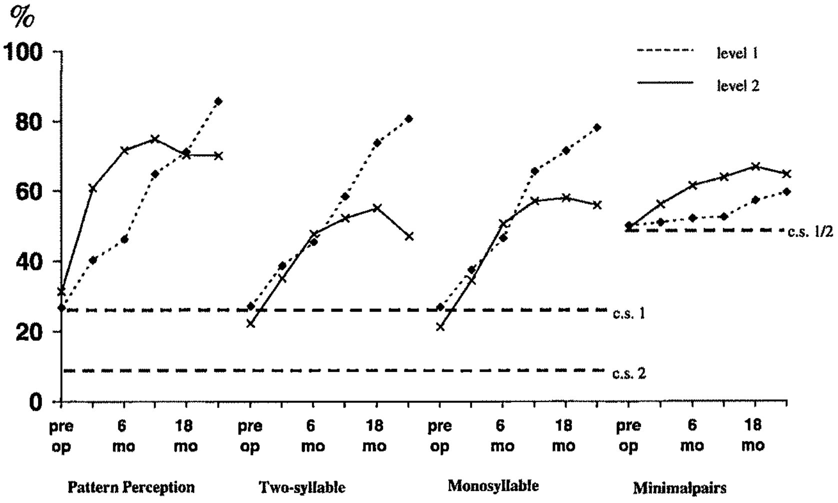


Fig 1. Level 1 and 2 scores for 4 closed-set tests. Chance scores for level 1 and 2 groups are labeled c.s. 1 and c.s. 2, respectively.

2). Although the 4-to-7 group initially have higher scores and also improve over time, the improvement is smaller at the later testing sessions. For those 3 test scores, the <4 group had an average score of 83% to 95% at 2 years postimplantation, while the 4-to-7 group scored between 63% and 76%. The 4-to-7 group scored slightly higher on the Minimal Pairs test for all test sessions.

Open-Set Tests. The open-set tests were more difficult than the closed-set tests, and thus the overall scores for both groups were lower (Fig 3 and Table 2). Nonetheless, both groups greatly improved after implantation. For all tests, the level 1 children had preimplantation scores near 0%, while the older children had slightly higher values, presumably because of hearing aid experience. The TAPS and monosyllable word test results look similar to the corresponding closed-set tests. The level 1 children steadily improved over the 2 years, reaching on average a score of about 55%, while the level 2 children (although having higher scores for the first year) plateaued after the first year, reaching scores between 40% and 45%. Thus, the level 1 children seem to surpass the older children by the 2-year test session, and this difference is expected to increase with time. It should be noted that words from the monosyllable word closed-set test sometimes appeared in the open-set version.

The GASP test was the only test on which the level 2 children had higher final scores than the younger group. This test required the child to answer questions; thus, developmental differences probably played a role in the low test scores of the level 1 group. Despite the initial low results, the level 1 children still made improvements after 6 months. For the more difficult common phrases (level 2) and Mr Potato Head (level 1) tests, it is evident again that as with the other tests, the younger children made greater improvements after about 6 months, while the older children made smaller improvements after 12 months.

When examining the results of the children of the <4 and 4-to-7 groups (Fig 4), we see the same trends as with the closed-set tests. The <4 group reach

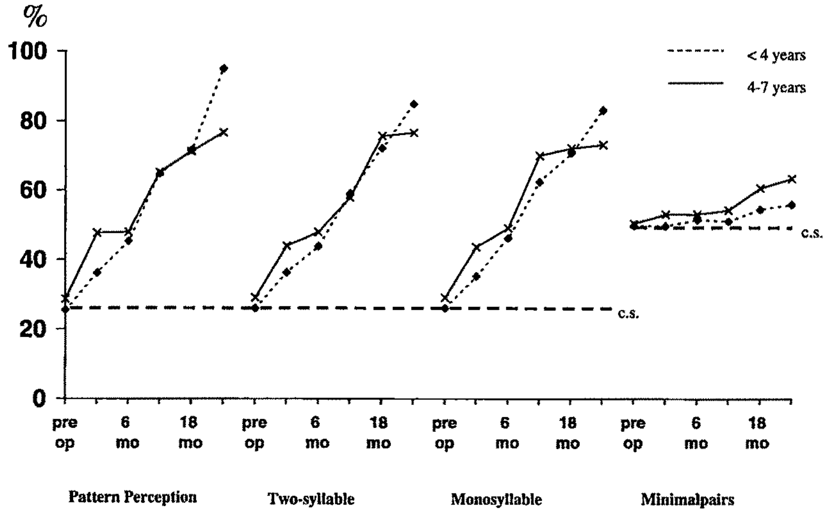


Fig 2. Closed-set results for children <4 years old and 4 to 7 years old. c.s. — chance level score.

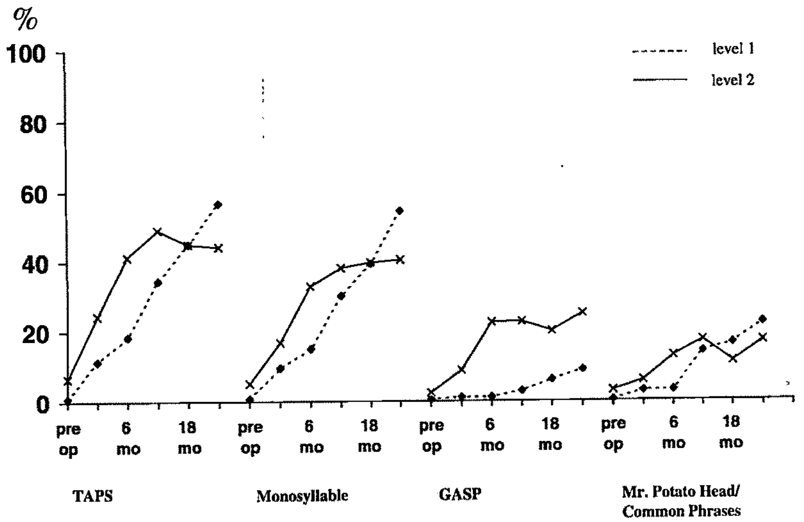


Fig 3. Level 1 and 2 scores for 4 open-set tests.

slightly higher scores on the TAPS and monosyllable tests (approximately 10%), although both groups show good improvement over time. The 2 groups showed similar scores for the GASP and Mr Potato Head tests.

DISCUSSION

The results of this study indicate that deaf children between the ages of 1 and 15 can benefit from a cochlear implant.[7] In general, the younger children (<7 years) made greater gains in speech perception than the older children (7 to 15 years). Although the older children tended to score higher preimplantation and initially after implantation due to early training and longer experience with hearing aids, the younger children improved more rapidly. Moreover, while the younger children steadily improved over time, the older children tended to plateau between 12 and 18 months after implantation. In particular, the children under 4 years old showed the greatest ability in developing their hearing and speech skills, reaching the highest results in the closed-set tests (except Minimal Pairs) and in the open-set TAPS and monosyllable word tests. On the other hand, the GASP and Mr Potato Head scores were low. However, these tests are quite difficult, sometimes using words that are not yet in a very young child's vocabulary. For these young children, we would then expect the results to increase with age.[8,9]

These results raise the question as to which age is ideal for cochlear implantation, and what results might be expected for older children. In general, implantation of congenitally and thus prelingually deafened children under the age of 7 years results in a considerably faster and more extensive speech development in the long run compared to older children. This improvement is most pronounced 6 to 18 months after surgery. On the basis of these results, we presume that the first phase of acoustic adaptation and processing of information takes place in the first 18 months after implantation for children without hearing aid experience but with rehabilitation. It is the opinion of this clinic that young deaf children

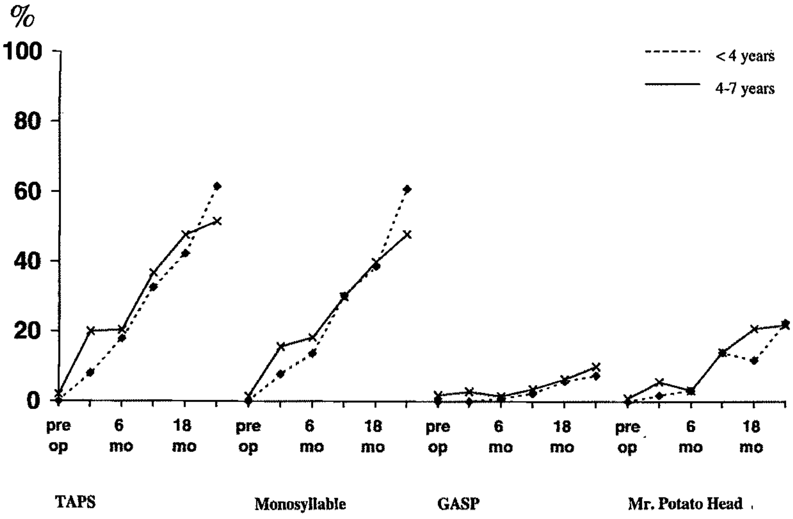


Fig 4. Open-set test results for children <4 years old and 4 to 7 years old.

need at least 2 or 3 years of rehabilitation to compensate for their lack of hearing and speech development. Therefore, since children often begin school at ages 6 to 7 years, implantation may be most appropriate when the child is under 4 years old. Then, these children have the opportunity to compensate for their delay in their speech development before they reach school age.[10,11] As stated by Osberger[1] and Lenarz et al,[11] there is a worldwide trend toward implanting children at increasingly younger ages, even below 2 years old.

Nonetheless, although early implantation is preferred, it must be noted that older children (7 to 15 years) do receive substantial benefit from a cochlear implant. The older children tend to make less progress, but still derive some important cues for hearing, such as rhythm and loudness. The benefit of a cochlear implant also plays a major role in increasing the child's self-confidence and improving psychosocial development. It also must be emphasized that aside from age, many other factors, such as preoperative mode of communication and family support, also influence clinical outcome.

For optimal results, an implanted child should be part of an intensive cochlear implant rehabilitation program for over 3 years. Ideally, children should receive about 12 weeks of concentrated hearing and speech therapy at an experienced center. Early detection of impairments in the auditory system and early use of hearing aid or a cochlear implant, together with intensive rehabilitation, provides the opportunity for a hearing-impaired child to attain near-normal speech development, as well as to attend a mainstream school.

REFERENCES

1. Osberger MJ. Current issues in cochlear implants in children. Hear Rev 1997;4:28-31.

2. Weber BP, Lenarz T, Neuburger J, von der Haar-Heise S, Dillo W, Battmer R-D. Clinical and experimental results relevant for implantation of Clarion cochlear implants in children. Adv Otorhinolaryngol 1997;52:282-5.

3. Osberger MJ, Soli S, von der Haar-Heise S. Comparative study of English and German-speaking children with the Clarion cochlear implant. Am J Otol 1997;18(suppl 6):164-5.

4. Erber NP. Auditory training. Washington, DC: Alexander Graham Bell Association, 1982.

5. Haskins H. A phonetically balanced test of speech discrimination for children [Thesis]. Evanston, Ill: Northwestern University, 1949.

6. Robbins AM. Mr Potato Head Task. Indianapolis, Ind: Indiana University of Medicine, 1993.

7. Zimmerman-Phillips S, Osberger MJ, Geier L, Barker M. Speech recognition performance of pediatric Clarion patients. Am J Otol 1997;18(suppl 6):153-4.

8. Tyler RS, Gantz BJ, Woodworth GG, Fryauf-Bertschy H, Kelsay DMR. Performance of 2- and 3-year-old children and prediction of 4-year from 1-year performance. Am J Otol 1997;18(suppl 6):157-9.

9. Löhle E, Falley U, Laszig R. Speech recognition in children with hearing aids versus results in children with implants. Am J Otol 1997;18(suppl 6):155-6.

10. Archbold S, Lutman ME, Marshall DH. Categories of auditory performance. Ann Otol Rhinol Laryngol [Suppl] 1995; 104(suppl 166):312-4.

11. Lenarz T, Battmer R, Bertram B. Cochlear implantation in children under the age of two. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

Ann Otol Rhinol Laryngol 108:1999

SPEECH PERCEPTION OF YOUNG CHILDREN USING NUCLEUS 22-CHANNEL OR CLARION® COCHLEAR IMPLANTS

NANCY M. YOUNG, MD
CHICAGO, ILLINOIS
VINCENT N. CARRASCO, MD
CHAPEL HILL, NORTH CAROLINA
KRISTINE M. GROHNE, MA
CHICAGO, ILLINOIS
CAROLYN BROWN, MS
CHAPEL HILL, NORTH CAROLINA

This study compares the auditory perceptual skill development of 23 congenitally deaf children who received the Nucleus 22-channel cochlear implant with the SPEAK speech coding strategy, and 20 children who received the CLARION® Multi-Strategy™ Cochlear Implant with the Continuous Interleaved Sampler (CIS) speech coding strategy. All were under 5 years old at implantation. Preimplantation, there were no significant differences between the groups in age, length of hearing aid use, or communication mode. Auditory skills were assessed at 6 months and 12 months after implantation. Postimplantation, the mean scores on all speech perception tests were higher for the Clarion group. These differences were statistically significant for the pattern perception and monosyllable subtests of the Early Speech Perception battery at 6 months, and for the Glendonald Auditory Screening Procedure at 12 months. Multiple regression analysis revealed that device type accounted for the greatest variance in performance after 12 months of implant use. We conclude that children using the CIS strategy implemented in the Clarion implant may develop better auditory perceptual skills during the first year postimplantation than children using the SPEAK strategy with the Nucleus device.

KEY WORDS — auditory skills, cochlear implant, children, speech coding strategy, speech perception.

INTRODUCTION

An increasing number of deaf children are being implanted at a young age with multichannel cochlear implant systems. The largest number of children with multichannel devices use the Nucleus 22-channel cochlear implant system with the SPEAK coding strategy, which became available in 1994. More recently, children have been implanted with the CLARION® Multi-Strategy™ Cochlear Implant, a device that received US Food and Drug Administration (FDA) approval for use in the pediatric population in June 1997. The Clarion provides 2 speech coding strategies: a simultaneous analog strategy and a nonsimultaneous pulsatile strategy termed Continuous Interleaved Sampler (CIS). This study examined the auditory perceptual skills of young children implanted with the Nucleus and Clarion devices and compared their performance at 6 and 12 months postimplantation.

TABLE 1. SUBJECT CHARACTERISTICS

	Nucleus *(N = 23)*	*Clarion* *(N = 20)*
Age at implantation (y; mean ± SD)	3.1 ± 1.0	3.3 ± 0.9
Length of hearing aid use (mo; mean ± SD)	19.3 ± 11.1	22.8 ± 10.6
Education (No. of subjects)		
Oral	11 (47.8%)	12 (60%)
Total communication	12 (52.2%)	8 (40%)

METHODS

All children were implanted at the Children's Memorial Medical Center in Chicago or the University of North Carolina in Chapel Hill. Children were included in the study if they met the following inclusion criteria: 1) under 5 years of age at time of implant surgery, 2) congenitally deaf, 3) radiographically normal cochleas as determined by computed tomography, 4) English as the primary language of the family, 5) absence of any medical condition likely

TABLE 2. NONZERO PREOPERATIVE SPEECH PERCEPTION SCORES

Subject No.	*ESP Pattern Perception*	*ESP Spondee*	*ESP Monosyllable*	*PB-K Phonemes*
Nucleus				
7	25			
13	50			
Clarion				
11	25	25	25	45
12	100	0	0	30
13	100	75	50	28
16	100	67	75	39

Data are percent correct.

From the Division of Pediatric Otolaryngology (Young) and the Department of Audiology (Grohne), Children's Memorial Medical Center, and the Department of Otolaryngology–Head and Neck Surgery, Northwestern University Medical School (Young), Chicago, Illinois, and the Division of Otolaryngology–Head and Neck Surgery (Carrasco, Brown) and the Carolina Children's Communicative Disorders Program (Brown), University of North Carolina School of Medicine, Chapel Hill, North Carolina.

CORRESPONDENCE — Nancy M. Young, MD, Division of Pediatric Otolaryngology, Children's Memorial Medical Center, 2300 Children's Plaza, #25, Chicago, IL 60614.

TABLE 3. SPEECH PERCEPTION TEST SCORES BY DEVICE

	Test	*Device*	*N*	*Mean*	*SD*	*Mean Rank*	*p*
6 Months	ESP Pattern Perception	Nucleus	19	30.5	37.2	16.2	.035
		Clarion	20	61.9	44.2	23.6	
	ESP Spondee	Nucleus	20	12.5	28.5	18.4	.161
		Clarion	20	37.1	47.2	22.7	
	ESP Monosyllable	Nucleus	19	6.2	23.1	16.9	.032
		Clarion	20	38.1	48.8	22.9	
	GASP Words	Nucleus	17	1.5	6.1	15.9	.074
		Clarion	18	17.6	33.7	20.0	
	GASP Sentences	Nucleus	17	0.6	2.4	16.9	.282
		Clarion	18	5.6	15.0	19.0	
	PB-K Phonemes	Nucleus	13	7.6	15.2	12.4	.095
		Clarion	16	20.9	24.6	17.1	
	PB-K Words	Nucleus	13	1.2	4.4	13.7	.159
		Clarion	17	5.7	15.2	16.9	
12 Months	ESP Pattern Perception	Nucleus	16	75.6	32.7	12.4	.083
		Clarion	12	95.8	8.4	17.3	
	ESP Spondee	Nucleus	16	56.3	48.6	12.6	.121
		Clarion	12	91.0	16.4	17.0	
	ESP Monosyllable	Nucleus	16	53.4	49.0	12.8	.178
		Clarion	12	92.1	8.1	16.8	
	GASP Words	Nucleus	8	4.1	8.9	4.7	.002
		Clarion	6	57.0	27.7	11.3	
	GASP Sentences	Nucleus	8	0.0	0.0	6.5	.090
		Clarion	6	15.0	25.1	8.8	
	PB-K Phonemes	Nucleus	12	29.6	31.0	8.5	.238
		Clarion	6	43.3	14.1	11.6	
	PB-K Words	Nucleus	12	13.0	26.0	8.3	.146
		Clarion	6	13.3	8.3	11.9	

to interfere with progress, and 6) speech coding strategy experience limited to SPEAK for the Nucleus 22 subjects or CIS for the Clarion subjects.

Forty-three children met the inclusion criteria. Twenty-three had been implanted with the Nucleus 22 implant, and 20 with the Clarion device. Subject characteristics — age at implantation, length of hearing aid use, and mode of education — are presented in Table 1. Children in the oral education group included those using auditory-oral, auditory-verbal, or cued speech communication methods during the first 12 months postimplantation.

Preimplantation, pure tone thresholds were evaluated unaided (with earphones) and aided (in sound field). Postimplantation thresholds were measured in sound field with the implant. Pure tone thresholds at 250 Hz, 500 Hz, 1,000 Hz, 2,000 Hz, and 4,000 Hz and a speech awareness threshold (SAT) were obtained for each child.

Closed-set speech perception testing both before and after implantation included the low verbal or standard version of the Central Institute for the Deaf Early Speech Perception (ESP) battery.[1] The protocol for testing open-set skills included the Glendonald Auditory Screening Procedure (GASP) words and sentences[2] and Phonetically Balanced-Kindergarten (PB-K) phonemes and words.[3]

DATA ANALYSIS

Children who were implanted with the Clarion during the FDA clinical trials period were administered all tests and were given a zero score for those tests on which they could not perform. However, Clarion children tested after termination of the investigational protocol, as well as Nucleus children, often were not given higher-level tests when they obviously did not have the necessary cognitive and linguistic skills. Therefore, no scores are available for those children on these tests. For the purposes of this study, children who had scores of zero on the ESP pattern perception and/or spondee tests and who were not given open-set tests were assigned a score of zero on the open-set tests. In addition, the 14 more recently implanted children had only 6-month data.

Descriptive and inferential statistical analysis was performed with a computer statistical package (SPSS for Windows). Parametric and nonparametric statis-

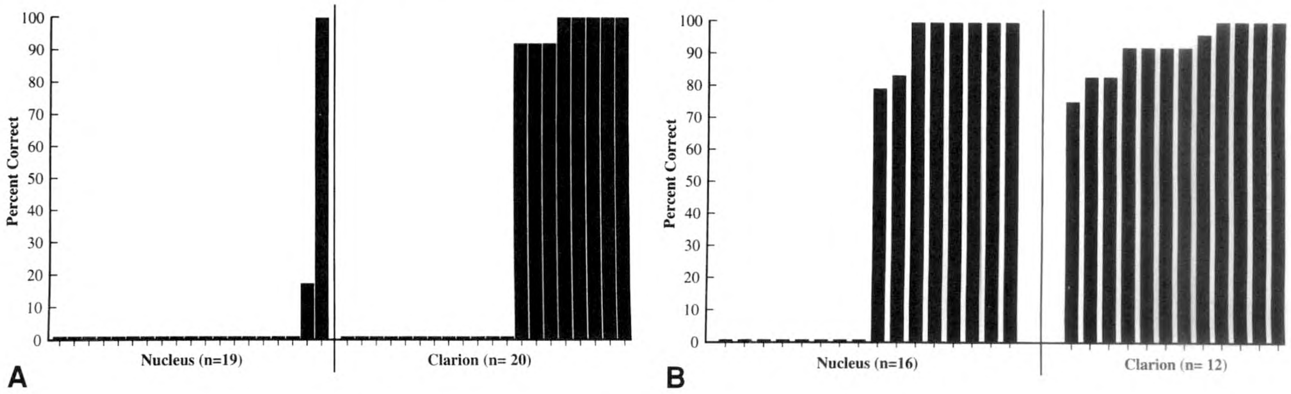


Fig 1. ESP Monosyllable test scores at A) 6 months and B) 12 months.

tics were used, as appropriate. Before performing independent group analyses to compare performance of the 2 device groups, Levene's test for equality of variances was applied. Because there were often significant differences in variance, most of the independent group comparisons for speech perception tests were performed with the nonparametric Mann-Whitney U test; *t*-tests were used to compare pure tone thresholds. Multiple regression analysis using a stepwise procedure was performed to examine the effects of preoperative differences between groups that might influence implant performance. For all analyses, the criterion for statistical significance was set at $p \leq .05$, 2-tailed.

RESULTS

There were no statistically significant differences between the Clarion and Nucleus groups for the 3 demographic characteristics listed in Table 1. Preimplantation, the Clarion group had better unaided thresholds at 1,000 and 4,000 Hz in comparison to the Nucleus group by 5 dB and 3 dB, respectively ($t = 2.1$, $p = .042$; $t = 2.17$, $p = .036$). With the implant, mean thresholds for all subjects ranged from 29 to 40 dB at 6 months and from 25 to 37 dB at 12 months, depending on test frequency. The only statistically significant difference between the 2 device groups was at 500 Hz, where the Clarion group had a better mean threshold by 4.6 dB at 6 months ($t = 2.19$, $p = .036$) and 3.6 dB at 12 months ($t = 2.08$, $p = .038$). Differences of similar magnitude approached significance for SAT at 6 months ($p = .084$) and 1 kHz at 12 months ($p = .053$), while the Nucleus group tended to show slightly better thresholds at 250 Hz at 6 months ($p = .061$).

Preimplant aided speech perception test results were not significantly different between the Clarion and Nucleus groups. Even so, for the ESP spondee, ESP Monosyllable, and PB-K phoneme tests, the Clarion group scores were higher and the difference approached but did not reach statistical significance ($p = .053$ for all 3 tests). However, 37 of 43 children were unable to score above zero on preoperative speech perception tests. Of the 6 children who did score above zero, the 4 with the best preoperative performance received the Clarion implant (Table 2).

Table 3 presents results of speech perception tests at 6 months and 12 months for the 2 device groups. Generally, the mean scores were higher for the Clarion group. These differences reached statistical significance for ESP Pattern Perception and ESP Monosyllables at 6 months, and for the GASP Word scores at 12 months. Other differences approached but did not reach significance (Table 3). Individual subject performance for the more difficult tests is shown in

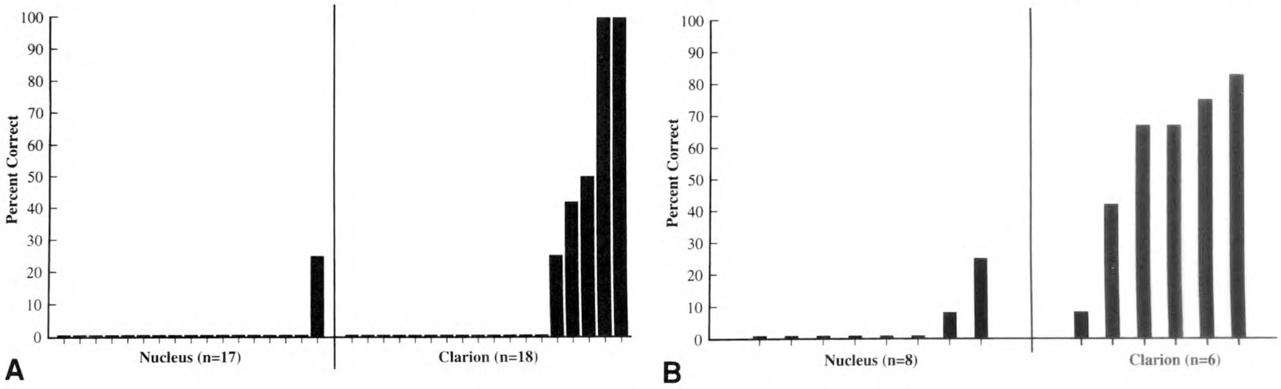


Fig 2. GASP Word scores at A) 6 months and B) 12 months.

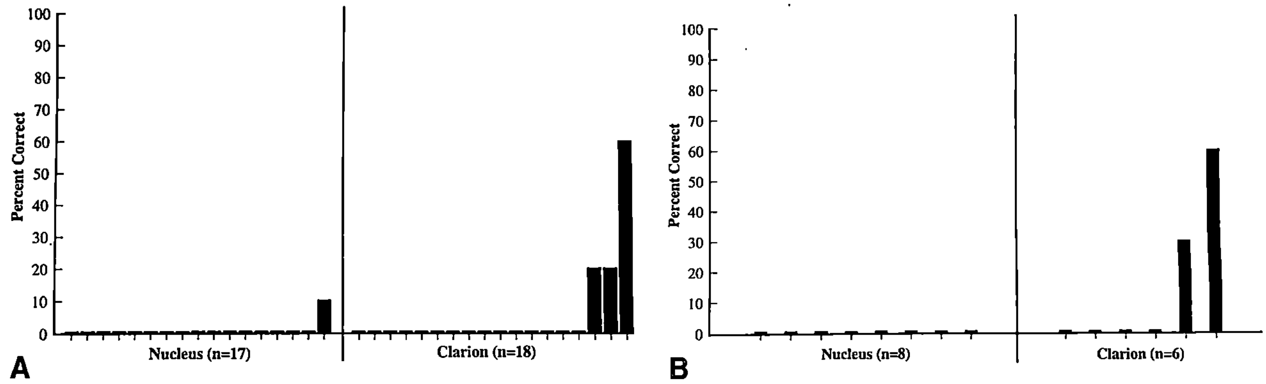


Fig 3. GASP Sentence scores at A) 6 months and B) 12 months.

Figs 1-4. Not all subjects were tested on every test, so the number of subjects is shown for each test. Bars represent scores above zero.

Because preimplant differences between the 2 groups may have influenced postoperative performance, the data were examined by multiple regression analysis. Independent variables included device, investigational site (Chicago or North Carolina), rehabilitation and communication method, age at surgery, months of hearing aid use, preoperative aided scores on the 3 ESP subtests, and aided PB-K phoneme score. Other open-set tests were not included because there was so little preoperative variability. Table 4 shows regression results for each speech perception test at 6 months and 12 months postimplantation. Preoperative variables that accounted significantly for a portion of the variance in postoperative scores are listed, as are the corresponding R^2 values. In general, preoperative aided SAT and/or ESP scores accounted for most of the variance in performance after 6 months of implant experience. However, the type of device accounted for the highest proportion of variance in performance at 12 months, even when the other factors were taken into account.

DISCUSSION

This study demonstrates that children implanted with the Clarion device and who use the CIS strategy may develop better auditory perceptual skills during the first year postimplantation than children implanted with the Nucleus 22 who use the SPEAK strategy. The results confirm the trends seen in a prior study of a smaller group of children implanted in Chicago at Children's Memorial Medical Center.[4] In that study, a trend toward better performance of Clarion children on the ESP subtests was noted.

Preoperatively, the Clarion group had lower aided thresholds at 2 frequencies, and more children in the Clarion group had nonzero scores on speech perception tests. This difference in the groups is not surprising in light of the expansion of candidacy criteria that permits implantation of children with higher degrees of speech perception skills who were not previously considered eligible for implantation. This situation raises the issue as to whether some children implanted more recently with the Clarion device are more likely to have better nerve survival. If so, they may be more likely to have improved performance regardless of which device is implanted. We attempted to address that possibility with the multiple regression analyses and found that device type still related significantly to the level of postimplant performance.

Notably, both the Clarion and Nucleus groups of children developed auditory skills at a more acceler-

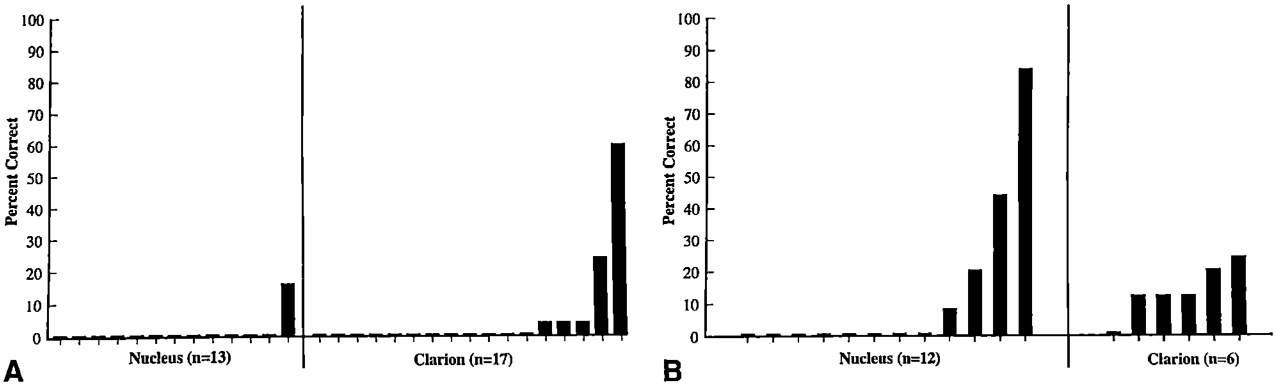


Fig 4. PB-K word scores at A) 6 months and B) 12 months.

TABLE 4. MULTIPLE REGRESSION ANALYSES OF SPEECH PERCEPTION PERFORMANCE

	Test	*Preoperative Predictors*	R^2	*p*
6 Months	ESP Pattern Perception	Aided SAT	.238	.005
	ESP Spondee	ESP Pattern, aided SAT	.517	.000
	ESP Monosyllable	ESP Pattern, aided SAT	.428	.000
	GASP Words	ESP Spondee	.865	.000
	GASP Sentences	ESP Pattern, ESP Spondee, ESP Monosyllable, PB-K Phonemes	.931	.000
	PB-K Phonemes	Investigational site, ESP Pattern		
	PB-K Words	ESP Pattern, ESP Monosyllable, ESP Spondee	.946	.000
12 Months	ESP Pattern Perception	Device	.169	.000
	ESP Spondee	Device	.203	.041
	ESP Monosyllable	Device	.243	.024
	GASP Words	Device	.686*	.000
		Education	.790	
	GASP Sentences	(Minimal variability)		
	PB-K Phonemes	Aided SAT	.279	.029
	PB-K Words	(No variability)		

*R^2 contributed by device alone.

ated rate than has been reported for children using previous-generation cochlear implant systems that implemented speech feature extraction strategies.[5-8] The CIS and SPEAK coding schemes, which attempt to encode the entire speech signal, appear to enable higher levels of performance than do feature extraction schemes. Children using those earlier strategies required at least 1 or more years of implant experience before closed-set discrimination skills emerged, and even longer experience was needed for open-set speech recognition skills to develop.[7]

However, there are significant differences between CIS and SPEAK coding strategies that may underlie the performance differences observed between the groups in the present study. The CIS is a pulsatile strategy that attempts to retain the fine temporal information in speech by providing a high rate of stimulation on all 8 available channels (800 pulses per second).[9,10] In contrast, SPEAK is a pulsatile strategy that encodes output only from the channels with the largest amplitudes or "maxima" and presents the information to selected electrodes at a lower stimulation rate (180 to 300 pulses per second).[11] The degree to which the device or speech coding strategy influences outcome remains an issue worthy of further study, especially because there are other differences in the design of these 2 implant systems, and because multiple non–device-related variables — including cognitive function and quality of postimplant habilitation — also can account for differences in performance.

ACKNOWLEDGMENT — We thank Karen Berliner, PhD, for her advice and assistance in the statistical analysis of the data.

REFERENCES

1. Geers AE, Moog JS. Evaluating speech perception skills: tools for measuring benefits of cochlear implants, tactile aids, and hearing aids. In: Owens E, Kessler DK, eds. Cochlear implants in young deaf children. Boston, Mass: College Hill, 1986: 227-56.

2. Erber N. Glendonald auditory screening procedure (the GASP). In: Auditory training. Washington, DC: AG Bell, 1982: 47-71.

3. Haskins HA. A phonetically balanced test of speech discrimination for children [Thesis]. Evanston, Ill: Northwestern University, 1949.

4. Young NM, Grohne K. A comparison of young children utilizing the Nucleus and Clarion cochlear implant systems. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

5. Fryauf-Bertschy H, Tyler RT, Kelsay DM, Gantz BJ, Woodworth GG. Cochlear implant use by prelingually deafened children: the influences of age at implant and length of device use. J Speech Lang Hear Res 1997;40:183-99.

6. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl 2):9-13.

7. Waltzman SB, Cohen NL, Gomolin RH, et al. Open-set speech perception in congenitally deaf children using cochlear implants. Am J Otol 1997;18:342-9.

8. Osberger MJ, Miyamoto RT, Zimmerman-Phillips S, et al. Independent evaluation of the speech perception abilities of children with the Nucleus 22-channel cochlear implant system. Ear Hear 1991;12(suppl):66S-81S.

9. Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. Nature 1991;352:236-8.

10. Wilson BS, Finley CC, Lawson DT, Wolford RD, Zerbi M. Design and evaluation of a continuous interleaved sampling (CIS) processing strategy for multichannel cochlear implants. J Rehabil Res Dev 1993;30:110-6.

11. Skinner MW, Clark GM, Whitford LA, et al. Evaluation of a new spectral peak coding strategy for the Nucleus 22-channel cochlear implant system. Am J Otol 1994;15(suppl 2):15-27.

Ann Otol Rhinol Laryngol 108:1999

COMPARISON OF SPEECH PERCEPTION IN PEDIATRIC CLARION® COCHLEAR IMPLANT AND HEARING AID USERS

MARIO A. SVIRSKY, PHD TED A. MEYER, MD, PHD

INDIANAPOLIS, INDIANA

Multichannel cochlear implants (CIs) allow many profoundly deaf children to achieve high levels of speech perception. In order to develop optimal criteria for implantation, it is crucial to test representative samples (or, if possible, full populations) of CI users and compare their results to those of hearing aid (HA) users of the same age and communication mode (oral or total communication) to determine which subgroups of HA users may obtain more perceptual benefit from a CI than from an HA. Word and phoneme identification skills of deaf children who use either HAs or CIs were evaluated and compared. The CI group included all of the prelingually deaf children in the United States who were implanted with the CLARION® Multi-Strategy™ Cochlear Implant during the clinical trial (as of January 1998). Before implantation, the mean scores on the PB-K test (scored phonemically) were lower for prospective CI users than for HA users. However, by 12 to 18 months postimplantation, the average scores for the CI users were higher than those of HA users with residual hearing in the 101– to 110–dB hearing level (HL) range. The CI scores were similar to those of HA users with residual hearing in the 90– to 100–dB HL range.

KEY WORDS — cochlear implant, hearing aid, prelingual deafness, speech perception.

INTRODUCTION

Multichannel cochlear implants (CIs) allow many people who became deaf as adults to recover the ability to understand speech without the aid of lipreading.[1,2] Most postlingually deafened adult CI users (ie, those who learned language before becoming deaf) can understand some speech without lipreading and can conduct fluent conversations with the aid of lipreading. The most successful adult CI users can communicate fluently over the telephone — a difficult task, because there are no visual cues to aid communication.

Although the use of CIs has been clearly successful in postlingually deafened adults, a growing body of data demonstrates that multichannel CIs also promote the development of speech perception and speech production in prelingually deafened children[3-5] (ie, those who are deaf at birth or become deaf before the age of 3). However, few studies have focused on a group of children that is particularly important — those who were implanted before the age of 6, and who have used a state-of-the-art stimulation strategy (SPEAK[1] or Continuous Interleaved Sampler [CIS][2]) since initial stimulation. This group is important for several reasons. First, children implanted before school age are more representative of the new demographics of cochlear implantation. Second, adult users of these stimulation strategies have achieved higher speech perception scores than users of older strategies,[1,2] so we may expect that children might achieve higher speech perception scores as well. And third, these children are more likely to achieve higher levels of speech perception, because they receive auditory input during the "critical period" for speech and language development.

In this study we have had the opportunity to examine data from all the prelingually deafened pediatric CI users who have been implanted in the United States with the CLARION® Multi-Strategy™ Cochlear Implant during the clinical trial and who use the CIS processing strategy. The focus of this study was the group of children implanted before the age of 6, but we also report results from those implanted between the ages of 6 and 12. We compared open-set word and phoneme recognition scores collected from those 2 groups of CI users and from hearing aid (HA) users with different amounts of residual hearing. This comparison is important because HAs represent an alternative to CIs, and a comparison study may help determine whether a candidate for cochlear implantation is likely to achieve more perceptual benefit from an HA or a CI. For example, in a previous study by Meyer et al,[6] it was determined that a group of CI users who predominantly employed older stimulation strategies achieved parity in speech perception scores with HA users who had losses in the 101– to 110–dB hearing level (HL) range after about 1 to 1.5 years of experience with the CI.

From the DeVault Otologic Research Laboratory, Department of Otolaryngology, Indiana University School of Medicine, Indianapolis, Indiana. This project was supported by grant DC00064 and training grant DC00012 from the National Institutes of Health/National Institute on Deafness and Other Communication Disorders.

CORRESPONDENCE — Mario A. Svirsky, PhD, DeVault Otologic Research Laboratory, Dept of Otolaryngology, Indiana University School of Medicine, 702 Barnhill Dr, RR-044, Indianapolis, IN 46202.

TABLE 1. NUMBER OF PARTICIPANTS BY COMMUNICATION MODE

Group	*OC*	*TC*	*Total*
Clarion (<6 y)	92	87	179
Clarion (6-12 y)	19	24	43
HA90-100	17	11	28
HA101-110	25	22	47
Total	153	144	297

OC — oral communication; TC — total communication; Clarion — Clarion cochlear implant users; HA90-100 — hearing aid users with unaided pure tone average in better ear of 90 to 100 dB hearing level; HA101-110 — hearing aid users with unaided pure tone average in better ear of 101 to 110 dB hearing level.

However, the CI users in the Meyer et al study did not quite reach the speech perception levels shown by HA users who had losses in the 90– to 100–dB HL range.

In addition, because it is important that clinicians working with a deaf child have valid information about the expected gains in communication for that child based on the child's age, residual hearing, assistive device, and communication mode, the comparisons between speech perception scores obtained by CI and HA users were performed separately for users of oral communication (OC) and total communication (TC; the simultaneous use of signed and spoken English).

METHODS

Hearing Aid Users. Seventy-five children with prelingual profound hearing losses (congenital or onset at less than 3 years of age) who use HAs participated in the study. The HA users were grouped in terms of their pure tone better-ear unaided thresholds at 500, 1,000, and 2,000 Hz. Participants were identified as H90-100 if their pure tone average (PTA) was between 90 and 100 dB HL, and HA101-110 if their PTA was between 101 and 110 dB HL. Of the 28 children with the most residual hearing (ie, HA90-100), 17 used OC and 11 used TC. Of the 47 children in the HA101-110 group, 25 used OC and 22 used TC (Table 1). The mean age at onset of deafness and age at the time the HAs were fitted did not differ as a function of HA group or communication mode (Table 2). The mean ages at testing for the HA90-100 group were 8.77 years for users of OC (range 4.8 to 15.3 years), and 8.72 for TC users (range 1.8 to 13.1 years). In the HA101-110 group, the mean ages at time of testing were 8.40 for the subjects who used OC (range 5.3 to 12.8 years) and 7.88 for TC users (range 4.6 to 11.5 years).

Cochlear Implant Users. Two hundred twenty-two children with prelingual profound hearing loss who received the Clarion multichannel CI participated in the study. This number included all children who received Clarion devices in the United States during the clinical trial and whose data were reported to the manufacturer as of early 1998. All of the children used the CIS processing strategy. One subject was excluded, because information about his communication mode was unavailable. One hundred eleven children used OC (including 14 subjects who used cued speech and 8 who received auditory-verbal training), and 111 used TC (including 1 subject who used only "natural" gestures, 1 subject who used mostly manual communication, and 1 subject who employed some cued speech at home). The age at onset of deafness was similar between the CI users and the HA users (Table 2). One hundred seventy-nine children were implanted prior to the age of 6 (92 used OC; 87 used TC), and 43 were implanted between the ages of 6 and 12 (19 used OC; 24 used TC). The average age at implantation was comparable for the children using OC or TC. For analysis purposes, CI users were grouped according to age at implantation (before 6 or between 6 and 12 years) and communication mode (OC or TC). Table 3 shows the mean age at testing for each subgroup at each

TABLE 2. AGE AT ONSET OF HEARING LOSS AND INITIAL FITTING WITH DEVICE

		Onset (y)		*Fitting (y)*	
Group		*OC*	*TC*	*OC*	*TC*
Clarion (<6 y)	Mean	0.3	0.2	3.2	3.3
	SD	0.6	0.5	1.1	1.2
	Range	0.0-2.5	0.0-2.5	1.6-5.8	1.5-5.9
Clarion (6-12 y)	Mean	0.2	0.5	8.2	8.5
	SD	0.5	0.8	2.0	1.6
	Range	0.0-1.5	0.0-2.5	6.1-11.9	6.2-11.5
HA90-100	Mean	0.1	0.5	1.9	1.4
	SD	0.3	0.8	1.1	0.9
	Range	0.0-1.0	0.0-2.5	0.2-5.0	0.3-3.0
HA101-110	Mean	0.2	0.4	1.4	1.3
	SD	0.5	0.8	1.6	0.7
	Range	0.0-2.4	0.0-3.0	0.3-2.7	0.1-3.0

TABLE 3. MEAN AGE AT TESTING (YEARS) FOR COCHLEAR IMPLANT USERS AT DIFFERENT INTERVALS

	Age at Implant <6 y		*Age at Implant 6-12 y*	
Interval (mo)	*TC*	*OC*	*TC*	*OC*
Preop	3.3	3.2	8.5	8.3
3	3.6	3.5	8.9	8.6
6	4.0	3.8	9.0	9.2
12	4.3	4.3	9.9	9.3
18	5.2	4.8		

test interval.

Testing Intervals. The time interval of testing and the number of children evaluated at each test interval varied. The CI users were tested before implantation and at 3, 6, 12, and 18 months after implantation. The children in the HA90-100 group were tested between 1 and 6 times, while the children in the HA101-110 group were tested between 1 and 4 times at 6-month or yearly intervals. The majority of both the HA users and the CI users were tested multiple times, although a few of the children were tested only once. Not every child was tested at every test interval, and there are few data at the 18-month interval.

Speech Materials. Although subjects were tested on a variety of speech perception materials, only the results from the Phonetically Balanced-Kindergarten Test (the PB-K test)[7] are reported here. The PB-K test is an open-set monosyllable word test. Words were presented to the children live-voice, with a mesh screen covering the mouth of the tester to obscure any visual cues. The children responded by repeating the word they heard. They also were allowed to sign when it was necessary to clarify the oral response. The test was scored for the number of words and phonemes correctly identified.

Statistical Analysis. The data from the HA users were analyzed to assess the effects of maturation (age) alone on speech perception scores. First, linear regressions were carried out separately for children using OC and TC in each of the HA groups (HA90-100 and HA101-110) for word and phoneme identification scores as a function of age at testing. The regressions provided estimates of the expected improvement in speech perception scores simply due to maturation and independent of CI use. When the linear regressions as a function of age were not statistically significant ($p > .10$), the mean score of the HA group was used as a benchmark for comparison with scores from CI users. Second, the speech perception scores of the CI users were compared to predicted scores for each HA group. The mean age for CI users at each test interval was determined, and the HA predictions were obtained with the linear regressions that had been carried out previously. In other words, the HA predictions were generated by setting the value of the independent variable (age at testing) to the mean age of each group of CI users at each test interval. All comparisons between scores from HA and CI users were conducted separately for children who used OC and TC.

Two sets of statistical analyses were performed. First, a Kruskal-Wallis 1-way analysis of variance (ANOVA) on ranks was performed on the data obtained from CI users to determine whether word and phoneme recognition scores became significantly higher with increased CI experience. This nonparametric test was used rather than the standard ANOVA because the data were not normally distributed. Second, we determined the 95% and the 99% confidence intervals for scores obtained by CI users at each test interval. These confidence intervals were compared to the mean scores predicted for HA users at the same age as the CI users, at each test interval.

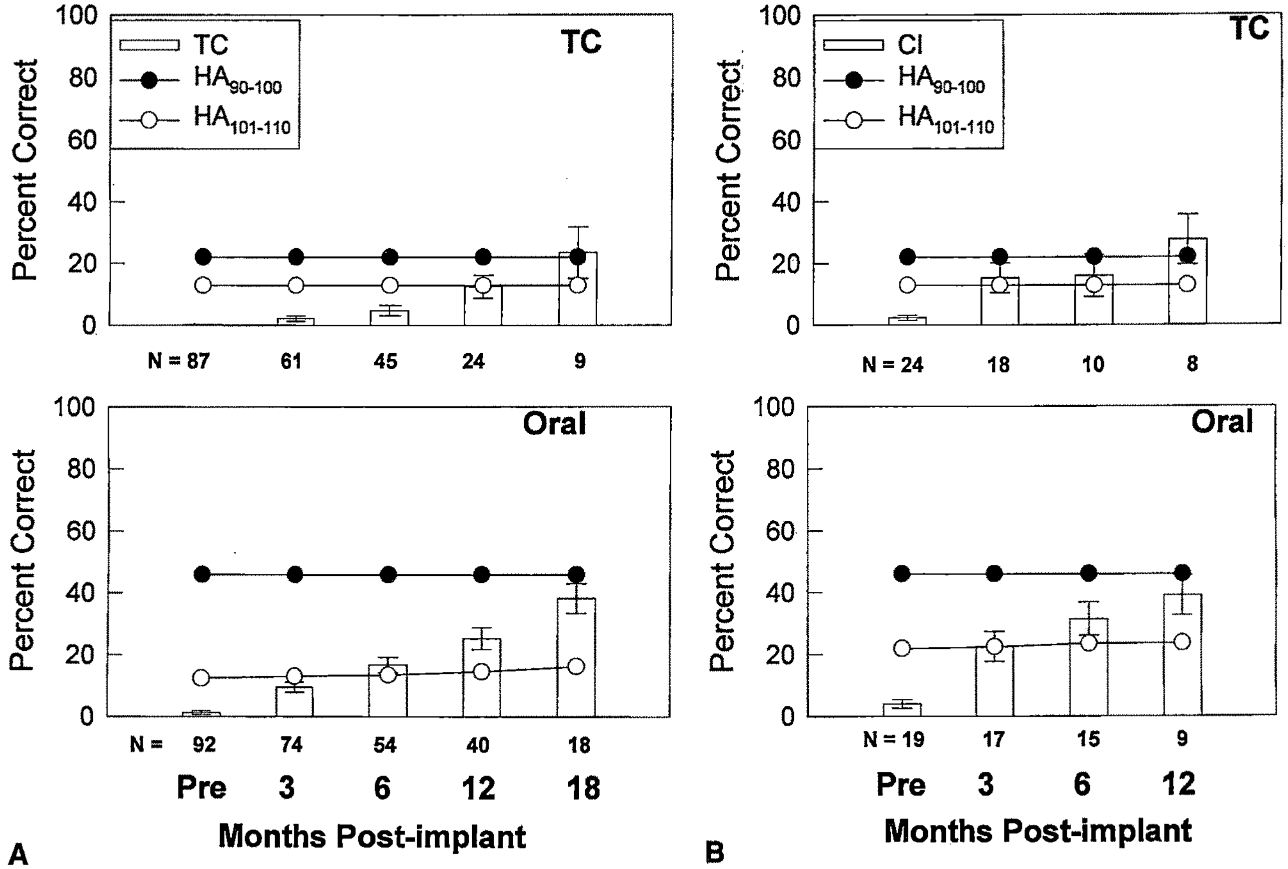
RESULTS

Hearing Aid Users. Linear regressions between the percentage of correct words and phonemes on the PB-K test versus the age at testing were carried out for the HA users grouped by the amount of residual hearing (HA90-100 or HA101-110) and the mode of communication (OC or TC). For the phoneme scores, none of the correlations were significant for any of the groups of HA users. The only group whose correlation between age at testing and PB-K phoneme scores approached significance were the users of OC in the HA101-110 group ($r = +.356$; $p = .068$). The pattern of correlations for word scores was similar.

Cochlear Implant Users. Phoneme recognition on the PB-K test improves with time for each of the 4 groups of CI users: children implanted before 6 or between 6 and 12 years, who used either OC or TC ($p < .001$; see Figure).

The top panel in the Figure, A, shows data for TC users implanted before the age of 6. Before implantation and up to 6 months postimplantation, the 99% confidence intervals for scores from CI users were below the comparison levels for both groups of HA users. However, by 12 months postimplantation, the scores for the CI users were not significantly different from the mean scores obtained from HA101-110 TC users. By 18 months postimplantation, there was no significant difference between the CI group and the HA90-100 group.

The bottom panel of the Figure, A, show a comparison of scores for OC users with CIs and with HAs. As with the TC users, scores for the CI users prior to implantation were significantly lower than



Percentage of phonemes correctly identified as function of months postimplantation for cochlear implant (CI) users A) implanted prior to age of 6 and B) implanted between 6 and 12 years of age. Data for children using total communication (TC) are plotted in top panels, and data for children using oral communication are plotted in bottom panels. Numbers under each bar indicate number of CI users tested at that particular interval. Black and white circles represent average predicted levels of hearing aid (HA) users in HA90-100 and HA101-110 groups, respectively. (HA90-100 is group with unaided pure tone average in better ear of 90 to 100 dB hearing level; HA101-110 is group with average of 101 to 110 dB.) These predictions were obtained from linear regression analysis based on average age of CI users at particular test interval. Error bars indicate standard error of mean.

the scores for both groups of children who used HAs. (The 99% confidence interval for CI scores was below both HA levels.) However, by 12 months postimplantation, the 99% confidence interval for CI users was above the HA101-110 level (although still below the HA90-100 level). By 18 months postimplantation, there was no significant difference between the mean scores for the CI users and those of the HA90-100 group. It should be noted that the scores for the HA users were obtained from children who were, on average, older than the CI users — a factor that tends to bias the comparison against the CI users. Nevertheless, the data suggest that CI users were able to match the speech perception skills of the HA90-100 group after only 18 months of implant use.

The data available for CI users implanted between the ages of 6 and 12 show a similar pattern (see Figure, B). Scores from CI users taken prior to implantation were significantly below the HA90-100 and the HA101-110 comparison levels. (Both HA levels were above the 99% confidence interval for CI users.) However, scores for CI users matched the HA101-110 levels in just 3 months postimplantation for users of both TC and OC. At 12 months postimplantation, scores for CI users exceeded the HA101-110 levels and matched the HA90-100 levels. Specifically, the HA90-100 levels fell within the 95% confidence intervals of scores for the CI users (both for OC and TC users), and in the case of OC users, the HA101-110 levels were below the 95% confidence intervals of the CI scores. In summary, the CI users performed well below both HA comparison groups prior to implantation, but they matched the average levels of the group with more residual hearing (the HA90-100 group) in as little as 12 months postimplantation.

Tables 4 and 5 show the PB-K word scores for users of OC and TC implanted before the age of 6, and between ages 6 and 12. Similar to the phoneme scores, PB-K word scores increased significantly over time for each of the 4 groups of CI users: children implanted before 6 or between 6 and 12 years, who used either OC or TC ($p < .001$). However, these

TABLE 4. MEAN PB-K WORD SCORES FOR COCHLEAR IMPLANT USERS IMPLANTED BEFORE AGE OF SIX

	OC			*TC*		
Interval (mo)	*N*	*PB-K Word*	*% of Scores >0*	*N*	*PB-K Word*	*% of Scores >0*
Preop	92	0.00	0.0	87	0.00	0.0
3	74	0.85	24.3	61	0.16	4.9
6	54	2.06	44.4	45	0.51	13.3
12	40	5.40	62.5	24	1.79	33.3
18	18	7.28	77.8	9	4.44	44.4

TABLE 5. MEAN PB-K WORD SCORES FOR COCHLEAR IMPLANT USERS IMPLANTED BETWEEN SIX AND TWELVE YEARS OF AGE

	OC			*TC*		
Interval (mo)	*N*	*PB-K Word*	*% of Scores >0*	*N*	*PB-K Word*	*% of Scores >0*
Preop	19	0.00	0.0	24	0.00	0.0
3	17	4.24	64.7	18	2.44	33.3
6	15	6.20	73.3	10	2.40	30.0
12	9	7.78	100	8	5.13	75.0

scores should be interpreted with caution, because many of the words in the PB-K test are not in the lexicons of these children.[8] Nevertheless, it is noteworthy that the CI users understood no words prior to implantation, and a clear majority were able to understand at least some words by 12 to 18 months postimplantation.

DISCUSSION

These results clearly suggest that on average, children with hearing losses in the 101– to 110–dB HL range (HA101-110 group) would receive greater speech perception benefits from a CI than they do from their HAs, irrespective of the mode of communication they are currently using. Although the speech perception skills of this group of HA users increase over time, they do not keep pace with the average gains achieved by children who receive a CI. The results from this study also suggest that many (and perhaps most) children with hearing losses in the 90– to 100–dB HL range would benefit from cochlear implantation. We predict that this trend will be verified further as the children in this study continue to be monitored and their open-set phoneme and word identification scores continue to increase.

The recommendations from the most recent NIH Consensus Conference on Cochlear Implants[9] suggest that children with profound (>90 dB HL) bilateral sensorineural hearing loss and minimal speech perception may be considered for cochlear implantation. Audiological and speech recognition criteria for implantation is an area that clearly warrants further examination, because the candidacy criteria will certainly change as the scientific knowledge in this area increases. The findings reported here, along with results from other research on prelingually deafened children, may be helpful in refining the audiological criteria, because they indicate which groups of potential CI users may obtain more benefit from a CI than they would from a conventional HA. One must remember, however, that audiological and speech recognition performance are only some of the criteria that play a role in determining CI candidacy. Children also should not have medical, surgical, radiological, or psychological contraindications to receiving a CI.

It is crucial to continue the evaluation of early-implanted children who have used state-of-the-art speech processing strategies exclusively. In this study, we did not attempt to compare explicitly the performance of our subjects (all of whom used the CIS strategy since initial stimulation) to users of previous generations of speech processing strategies. However, it is interesting to note that a group of CI users who, for the most part, employed older stimulation schemes such as MPEAK[10] and F0-F1-F2,[11] took between 3 and 5 years to even approach the speech perception levels of the HA90-100 group.[6] Furthermore, in the study of Meyer et al,[6] CI users did not reach the levels of speech perception achieved by the HA90-100 group even after 3 to 5 years. In contrast, CI users of the Clarion CIS strategy required only 12 to 18 months to match and sometimes exceed the phoneme identification scores shown by the HA90-100 group.

Future research should assess the speech perception levels that can be achieved ultimately by early-implanted pediatric users of state-of-the-art stimulation strategies. Moreover, it now may become important to compare their speech perception to that of children with hearing impairment in the severe range (70 to 90 dB HL), some of which may become candidates for cochlear implantation in the future.

ACKNOWLEDGMENTS — The authors thank Drs Mary Joe Osberger and Laurel Fisher for providing the data from cochlear implant users, which were collected at 35 institutions as part of the pediatric clinical trial of the Clarion cochlear implant.

REFERENCES

1. Skinner MW, Clark GM, Whitford LA, et al. Evaluation of a new spectral peak coding strategy for the Nucleus 22 channel cochlear implant system. Am J Otol 1994;15:15-27.
2. Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. Nature 1991;352:236-8.

3. Tyler RS, Fryauf-Bertschy H, Gantz BJ, Kelsay DM, Woodworth GG. Speech perception in prelingually implanted children after four years. Adv Otorhinolaryngol 1997;52:187-92.

4. Osberger MJ, Miyamoto RT, Zimmerman-Phillips S, et al. Independent evaluation of the speech perception abilities of children with the Nucleus 22-channel cochlear implant system. Ear Hear 1991;12(suppl):S66-S80.

5. Waltzman S, Cohen NL, Spivak L, Ying E, Shapiro W, Hoffman R. Improvement in speech perception and production abilities in children using a multichannel cochlear implant. Laryngoscope 1990;100:240-3.

6. Meyer TA, Svirsky MA, Kirk KI, Miyamoto RT. Improvements in speech perception in prelingually-deafened children: effects of device, communication mode, and chronological age. J Speech Lang Hear Res 1998;41:846-58.

7. Haskins H. A phonetically balanced test of speech discrimination for children [Thesis]. Evanston, Ill: Northwestern University, 1949.

8. Kirk KI, Pisoni DB, Osberger MJ. Lexical effects on spoken word recognition by pediatric cochlear implant users. Ear Hear 1995;16:470-81.

9. NIH Consensus Conference. Cochlear implants in adults and children. JAMA 1995;274:1955-61.

10. Skinner MW, Holden LK, Holden TA, et al. Performance of postlinguistically deaf adults with the Wearable Speech Processor (WSP III) and Mini Speech Processor (MSP) of the Nucleus multi-electrode cochlear implant. Ear Hear 1991;12:3-22.

11. Blamey PJ, Dowell RC, Clark GM, Seligman PM. Acoustic parameters measured by a formant-estimating speech processor for a multiple-channel cochlear implant. J Acoust Soc Am 1987;82:38-47.

Ann Otol Rhinol Laryngol 108:1999

SPEECH PRODUCTION RESULTS IN CHILDREN IMPLANTED WITH THE CLARION® IMPLANT

CAROLYN BROWN, MS DEBORAH W. MCDOWALL, MA
CHAPEL HILL, NORTH CAROLINA

Speech production changes were examined in 24 profoundly hearing-impaired children following implantation with the CLARION® Multi-Strategy™ Cochlear Implant. All study participants were implanted below the age of 6, and with 1 exception, the children were congenitally deaf, with little or no auditory experience prior to implantation. A within-subjects design was used in which the children's preoperative speech skills with hearing aids were compared to postoperative performance with the Clarion after 3 and 6 months of implant use. Production skills were evaluated with a measure designed specifically to assess hearing-impaired children's spontaneous use of early developing phonological patterns in words. The results revealed significant improvement over time in 8 of the 9 speech features examined. The greatest improvement occurred between the 3- and 6-month postoperative intervals, with more limited improvement evident between the preimplant and 3-month time periods. The results demonstrate that significant improvements occur in speech production skills in very young children with congenital deafness after they have used current implant technology for a relatively limited amount of time.

KEY WORDS — children, cochlear implants, speech production.

INTRODUCTION

Previous research has shown that cochlear implants promote speech production skills in profoundly deaf children. Following implantation, improvements have occurred in children's phonetic repertoires, imitative production of nonsegmental and segmental features of speech, and overall intelligibility.[1-10] These studies, however, examined the performance of children using earlier implant technology, which consisted of single-channel devices or multichannel implants that employed a feature-extraction strategy. More substantial improvements in speech production might occur with current implants that encode the entire speech signal rather than specific, limited speech features. In addition, candidacy criteria have changed over time. A growing trend is to implant children at a very young age to provide access to sound during critical learning periods.[11] Today, the majority of children are implanted at or below the age of 4. Moreover, most of these children are congenitally deaf, with little or no auditory experience prior to implantation.

The purpose of this study was to examine changes in speech production over time in young children implanted with the CLARION® Multi-Strategy™ Cochlear Implant. A within-subjects design was employed to compare preoperative performance with hearing aids to postoperative performance with the Clarion device after 3 and 6 months of device use. Unlike most previous studies that examined production of nonsegmental and segmental (consonant and vowel) features in nonsense syllables, the present study examined these speech skills in words and rated the children's productions for accuracy in the representation of specific phonological patterns and acoustic features.

METHODS

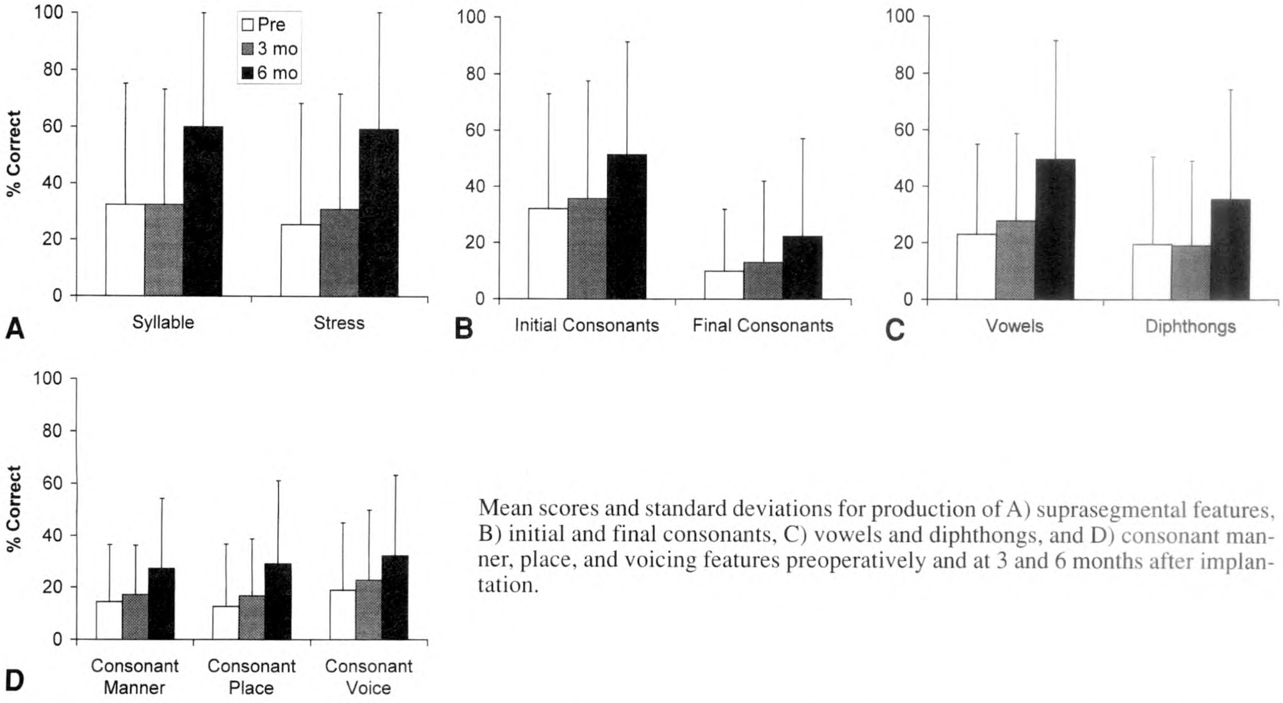
Participants. Twenty-four children with profound hearing impairments participated in the study. Deafness was congenital in 23 of the children and acquired at age 14 months in the remaining child. All children were implanted with the Clarion cochlear implant because they received negligible functional benefit from conventional hearing aids. The mean preimplant pure tone average was 112 dB hearing level (HL) in the implant ear and 109 dB HL in the nonimplant ear. The mean age at implantation was 3.6 years (range 1.9 to 5.9 years). Preoperatively, 6 children used total communication, 8 used cued speech, 3 were in auditory-oral programs, and 7 used an auditory-verbal approach. However, half of the children using total communication were changed to either auditory-oral or auditory-verbal approaches immediately after implantation. The cause of deafness was unknown in 83% of this group. The remaining causes were heredity, Waardenburg's syndrome, and cytomegalovirus. All children were programmed with the Continuous Interleaved Sampler (CIS) speech processing strategy.

Speech Materials and Procedures. The assessment procedure used was Identifying Early Phonological Needs in Children with Hearing Impairment (IEPN),

---

From the North Carolina Children's Communicative Disorders Program, Division of Otolaryngology–Head and Neck Surgery, University of North Carolina, Chapel Hill, North Carolina.

CORRESPONDENCE — Carolyn Brown, MS, North Carolina Children's Communicative Disorders Program, ENT Clinic, Ground Floor, Neurosciences Hospital, University of North Carolina, Manning Drive, CB #7600, Chapel Hill, NC 27514.



Mean scores and standard deviations for production of A) suprasegmental features, B) initial and final consonants, C) vowels and diphthongs, and D) consonant manner, place, and voicing features preoperatively and at 3 and 6 months after implantation.

developed by Paden and Brown.[12] This procedure was designed as a clinical tool to assess early phonological processes. Therefore, it samples broader categories of speech — not every phoneme. The stimuli consist of 25 words that are presented in line-drawn picture form. Word pattern scores are obtained for accuracy in syllable number and stress, as well as presence of initial and final consonants. Vowels and diphthongs are scored on the basis of height and place accuracy. An example of the vowel rating scale would be as follows: minus (–) = no vowel produced; 0 = vowel present, but not produced in the correct area of the mouth (fet for feet); 1 = vowel present and produced in the correct area of the mouth, but not the correct vowel (fit for feet); 2 = correct vowel with distortion (feet with nasalization); and 3 = completely correct vowel production. Consonants are rated for correctness of manner, place, and voicing characteristics. Scoring for consonant manner would be as follows: minus (–) = no consonant produced; 0 = present but incorrect in manner (eg, /t/ for /s/ or plosive for fricative); 1 = present, correct in manner, but incorrect phoneme (eg, /f/ for /s/); 2 = present, correct phoneme, but distorted (lateralized /s/); and 3 = completely correct consonant.

For each child, an elicited response was attempted for each word. However, if it was not produced correctly or at all, a model was presented in an effort to obtain an imitative response. The child's best response was scored for this study.

RESULTS

The results were subjected to a repeated-measures analysis of variance to examine changes in speech production skills over time. The Figure, A, shows the mean score (percent) and standard deviation on the suprasegmental features preoperatively with hearing aids and 3 and 6 months postimplantation. There was a significant improvement in performance over time (F(2,24) = 6.22; $p < .01$) in syllable production. Although there was no change in the mean syllable score between the preimplant and 3-month intervals, the mean score improved to 60% at the 6-month interval, representing an average improvement of 28% over the 6-month period of time. The Figure, A, also displays the results in production of the stress feature. The results of the analysis revealed a significant improvement in the children's production of this feature over time (F(2,24) = 6.82; $p < .001$). Again, there was negligible change between the preimplant and 3-month intervals, but the mean 6-month score improved to 59% from a mean score of 25% preoperatively.

The Figure, B, shows the results for the presence of initial and final consonants. Comparison of the 2 data sets reveals a greater improvement in the production of initial consonants than in that of final consonants. Production of initial consonants increased significantly over time (F(2,24) = 2.28; $p < .05$). There was negligible change in the occurrence of initial consonants at the 3-month interval, but after 6 months of implant use, the mean score increased to 51% from a preoperative mean level of 32%. The improvement in final consonant production approached but did not reach statistical significance (F(2,24) = 3.23; $p < .06$). After 6 months of Clarion use, the mean score was 22%, representing a 12% increase compared to the preoperative mean score.

The Figure, C, summarizes the results for vowels and diphthongs. Accuracy of vowel production increased from a mean score of 23% preoperatively to a mean score of 50% at the 6-month interval. Improvement in vowel production was statistically significant over time ($F(2,24) = 8.05$; $p < .01$). Production of diphthongs also improved significantly over time ($F(2,24) = 3.81$; $p < .05$), with an increase in the mean score from 20% preoperatively to a mean score of 35% after 6 months of Clarion use. Production of both vowels and diphthongs improved more between the 3- and 6-month intervals than between the preimplant and 3-month time periods.

The results for consonant manner, place, and voicing are shown in the Figure, D. Accuracy of production of the manner feature improved significantly over time ($F(2,24) = 9.83$; $p < .001$). Preoperatively, the mean consonant manner score was 14%, which increased to a mean score of 27% at the 6-month postoperative interval. Similar improvement occurred in the production of consonant place. The mean score preoperatively was 13%, compared with a mean score of 29% at the 6-month postoperative interval. Production of consonant voicing also increased significantly over time ($F(2,24) = 5.82$; $p < .01$). The mean score increased from 19% preoperatively to 32% after 6 months of implant use. The consonant features showed the same pattern of change observed for the other features. That is, more substantial improvement occurred between the 3- and 6-month intervals than between the preimplant and 3-month intervals.

DISCUSSION

The results revealed that significant changes occurred in the speech production skills of children implanted with the Clarion device after only 6 months of device use. Moreover, speech improvements were observed in very young children who (with 1 exception) were congenitally deafened, with little or no auditory experience prior to implantation. The greatest gains in speech production occurred in the production of nonsegmental features (syllable number and stress patterns) and in the production of vowels and diphthongs. Improvement in consonant features was more limited during the period of this study (ie, 6 months). Continued improvement in all speech skills, especially in consonant production, is predicted to occur with more extended implant experience. The results of this study are difficult to compare with previous results because of differences in subject characteristics, testing materials, and data reporting. Nevertheless, these results clearly demonstrate that substantial improvements occur in speech production after relatively limited implant use.

Finally, these data contribute new findings regarding the production of speech features in words by implanted children. Most previous studies have examined production skills for nonsense syllables, and generalization to words is difficult. The use of the IEPN also provides information specific to acoustic features of speech.

REFERENCES

1. Kirk KI, Brown C. Speech and language results in children with a cochlear implant. Ear Hear 1985;6(suppl):36S-47S.

2. Osberger MJ, Robbins AM, Berry SW, Todd SL, Hesketh LJ, Sedey A. Analysis of spontaneous speech samples of children with cochlear implants or tactile aids. Am J Otol 1991;12 (suppl):151-64.

3. Tobey EA, Angelette S, Murchison C, et al. Speech production performance in children with multichannel cochlear implants. Am J Otol 1991;12(suppl):165-73.

4. Tobey EA, Hasenstab S. Effects of Nucleus Multichannel cochlear implant upon speech production in children. Ear Hear 1991;12(suppl):48S-54S.

5. Osberger MJ, Maso M, Sam LK. Speech intelligibility of children with cochlear implants, tactile aids, or hearing aids. J Speech Hear Res 1993;36:186-203.

6. Tobey EA, Geers A, Brenner C. Speech production results and speech feature acquisition. Volta Rev 1994;96:109-30.

7. Osberger MJ, Robbins AM, Todd SL, Riley AI, Miyamoto RT. Speech production skills of children with multichannel cochlear implants. In: Hochmair-Desoyer IJ, Hochmair ES, eds. Advances in cochlear implants. Vienna, Austria: Manz, 1994:503-8.

8. Kirk KI, Diefendorf E, Riley A, Osberger MJ. Consonant production by children with multichannel cochlear implants or hearing aids. Adv Otorhinolaryngol 1995;50:154-9.

9. Grogan ML, Barker EJ, Dettman SJ, Blamey PJ. Phonetic and phonologic changes in the connected speech of children using a cochlear implant. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):390-3.

10. Robbins AM, Kirk KI, Osberger MJ, Ertmer D. Speech intelligibility of implanted children. Ann Otol Rhinol Laryngol [Suppl] 1995;104(suppl 166):399-401.

11. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl 2):9-13.

12. Paden EP, Brown CJ. Identifying early phonological needs in children with hearing impairment. Washington, DC: AG Bell Association, 1990.

LANGUAGE DEVELOPMENT IN CHILDREN IMPLANTED WITH THE CLARION® COCHLEAR IMPLANT

AMY MCCONKEY ROBBINS, MS
INDIANAPOLIS, INDIANA

PRISCILLA M. BOLLARD, EDD
NEW YORK, NEW YORK

JANET GREEN, MS
NEW YORK, NEW YORK

This study examined the development of language skills in 23 prelingually, profoundly deaf children following implantation with the CLARION® Multi-Strategy™ Cochlear Implant. Language skills were assessed with the Reynell Developmental Language Scales (RDLS) preoperatively with hearing aids, and compared to postoperative performance after 6 months of Clarion use. The RDLS was administered in each child's preferred mode of communication, either spoken English alone or simultaneous spoken and signed English. Significant improvements were observed in average age-equivalent scores over time, both for receptive and expressive skills, although the absolute language levels of the implanted children remained delayed relative to those of hearing peers of the same chronological age. The children's rate of language growth in the first 6 months of implant use also was calculated. The results from this analysis showed that the Clarion children, on average, progressed at a rate that exceeded that of normal-hearing children of the same language age. There was no significant difference between the language performance of children who used oral versus total communication.

KEY WORDS — children, cochlear implant, language.

INTRODUCTION

Children with profound hearing loss historically have experienced significant delays in all facets of English language development. In addition, the language deficits of profoundly hearing-impaired children become more pronounced as they grow older.[1-3] Deaf children fall further behind their hearing peers with increasing age, presumably because the later-evolving linguistic skills require more complex syntactic forms, increased vocabulary, and more abstract concepts than early-emerging skills.

Multichannel cochlear implants have been shown to enhance language learning in the children who receive them.[4-7] However, an important issue in determining the efficacy of cochlear implants in promoting language development is the analysis method used to document this benefit. If a test standardized on children with normal hearing is used to assess language skills, then performance is typically expressed in terms of an age-equivalent (ie, language age) score. For example, an age-equivalent score of 48 months implies that the child has the language skills (or language age) equivalent to that of a normally developing 4-year-old child, at least for those skills measured on the test of interest. Previous research has shown substantial improvements in age-equivalent scores in children following implantation.[4] Moreover, the results of this research indicated that even though the language of the implanted children remained delayed relative to their age-matched peers, the difference between their skills and those of their normal-hearing peers remained stable, rather than increasing over time.

Although age-equivalent scores provide important information regarding the performance of profoundly hearing-impaired children relative to their peers with normal hearing, this type of analysis fails to provide comprehensive information on the change in language skills relative to the child's abilities prior to implantation. Another approach that provides more meaningful information about language development involves measurement of the rate of language change that occurs over a specified period of time following implantation. This approach provides information on the change in age-equivalent scores relative to the period of time during which the change occurred.

Examination of the rate of language growth has been employed in several recent investigations with pediatric cochlear implant patients.[5,6] After 1 year of device use, children wearing the Nucleus implant were observed to learn language at a rate equivalent to that of children with normal hearing, that is, approximately 12 months of language growth in 12 months' time. In addition, the rate of language learning of the implanted children was substantially faster

---

From Communication Consulting Services, Indianapolis, Indiana (Robbins), and Lenox Hill Hospital (Bollard) and the Department of Otolaryngology, New York University Medical Center (Green), New York, New York. Portions of the work at Lenox Hill Hospital were supported by the Deafness Research Foundation.

CORRESPONDENCE — Amy McConkey Robbins, MS, Communication Consulting Services, 8512 Spring Mill Rd, Indianapolis, IN 46260.

than that of their profoundly hearing-impaired peers who wore conventional hearing aids, even though the absolute language scores of the implanted children remained delayed relative to that of their normal-hearing peers of the same chronological age.

Rate of language learning also was used to measure implant benefit across a number of subskills that constitute language competence.[7] Aspects of linguistic development found to be enhanced by cochlear implants included receptive and expressive vocabulary and expressive concepts. Implanted children's comprehension of grammatical forms, including syntax and morphology, were not found to improve at the rate seen for other subskills. The studies cited above examined language development in children implanted with the Nucleus 22-channel cochlear implant, with the majority of the children using previous-generation speech-extraction speech processing strategies (F0-F1-F2 and MPEAK). There are, however, no published reports on the change in language with current implant technology.

The present study was carried out to address 2 issues. One purpose was to examine language changes that occur in children implanted with the CLARION® Multi-Strategy™ Cochlear Implant. A second goal was to examine postoperative language changes as a function of preoperative communication mode. Earlier studies have shown that preoperative communication mode contributes to differences in the speech perception performance of children with implants.[8-10] In contrast, previous studies of language development have not found communication mode to be a significant predictor of postimplant language performance.[6,7] A possible explanation for the difference in results is that only auditory skills were assessed in the speech perception studies, whereas the language studies employed the child's preferred mode of communication (ie, signs, speech, and audition for children who used total communication [TC]; and speech, audition, and speechreading for the oral children). The rationale for this approach is that language development is a multisensory phenomenon that is influenced by more than just auditory input. Thus, the most appropriate method to assess language skills in children who use TC is with signs in addition to speech and audition, given that these communication modes reflect their exposure to language in everyday situations. Similarly, children in oral communication (OC) programs have access to lipreading in addition to audition in their everyday language-learning environments. Therefore, the present investigation also examined language abilities by means of communication strategies that approximated the children's everyday learning environments (ie, in each child's preferred communication mode).

METHODS

Subjects. Twenty-three children wearing the Clarion cochlear implant system served as subjects. All subjects were prelingually deafened, with an average age at onset of deafness of 1 month (range birth to 20 months). The average age at time of implantation was 3 years 2 months (range 24 to 65 months). The children used English as their native language. Fifteen of the children used OC, and 8 used TC (simultaneous spoken English and Signing Exact English[11]). The mean preimplant unaided pure tone average (PTA) in the implant ear was 112 dB hearing level (HL). The mean preimplant unaided PTAs of the OC and TC groups were 110 and 116 dB HL, respectively.

Test Instrument. The Reynell Developmental Language Scales, Revised (RDLS)[12] were used to evaluate the English-language skills of the children. This evaluation tool is standardized on a broad sample of children with normal hearing, allowing comparison of implanted children to their hearing peers. The RDLS measures receptive and expressive language skills independently, yielding separate age-equivalent scores for comprehension and production. The Reynell has been used to assess language skills of children with profound hearing impairments in previous studies.[1,6,13] The format of the test involves object manipulation, comprehension of instructions, and the ability to understand and produce utterances of increasing length and complexity. Because the question type and response format varies throughout the test, the RDLS reflects real-world communication to a greater degree than do many other language tests that involve, for example, multiple-choice picture-pointing responses.[14] The test may be administered in the child's preferred communication mode, including spoken English alone, spoken plus signed English, or spoken English plus cued speech.

Data Collection. The RDLS was administered to each of the children preoperatively while they were using hearing aids, and approximately 6 months after receiving their Clarion implant. All children used the Continuous Interleaved Sampler (CIS) speech processing strategy. Each child's raw score on the receptive and expressive sections of the RDLS was converted to a language age in months (ie, age-equivalent score). As noted above, the test was administered in the child's typical communication mode. Thus, for children who used TC, the results reveal underlying English language competence, and not necessarily spoken language competence.

Data Analysis. Two methods were used to analyze the changes in age-equivalent language scores that occurred following implantation. Analysis 1 in-

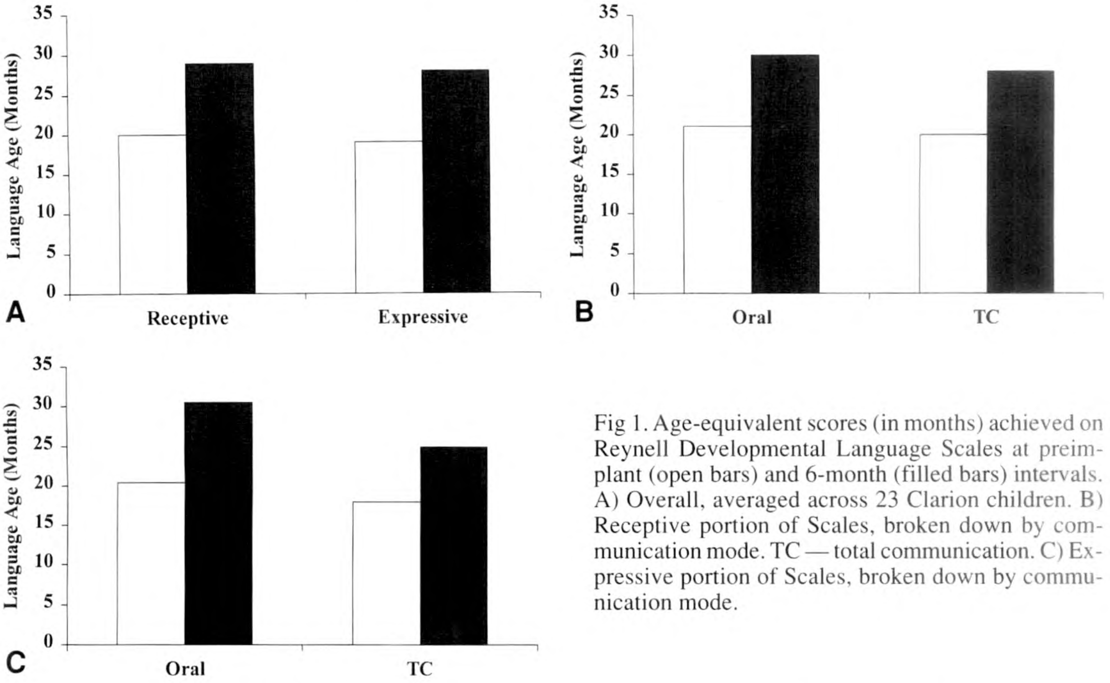


Fig 1. Age-equivalent scores (in months) achieved on Reynell Developmental Language Scales at preimplant (open bars) and 6-month (filled bars) intervals. A) Overall, averaged across 23 Clarion children. B) Receptive portion of Scales, broken down by communication mode. TC — total communication. C) Expressive portion of Scales, broken down by communication mode.

volved comparison of the *absolute age-equivalent scores* obtained at the preimplant and 6-month intervals. Analysis 2 measured the children's *rate* of growth in months for receptive and expressive language. For this second analysis, the amount of language change is expressed as rate of improvement within a given period of time. To calculate rate of language growth, the change in Reynell age-equivalent scores that occurred between the 2 test intervals was divided by the actual amount of time that passed between those intervals. (The average amount of time that elapsed between test intervals was 6.6 months [range 4.7 to 8.4 months] because of scheduling issues and other considerations.) This calculation then was converted to percent. For example, a child who made 5 months of language growth in 6 months' time would receive a growth rate score of 83%: (5/6)100. A growth rate of 6 months' language improvement in 6 months' time — 100% — would indicate developmental language growth equivalent to that seen in children with normal hearing of the same language age.

Repeated-measures analysis of variance was performed to analyze the results, with interval as the within-subjects variable and communication mode as the between-subjects variable. Separate analyses were performed to examine the absolute age-equivalent scores and the rate of language improvement.

RESULTS

Age-Equivalent Performance. Figure 1A shows the average age-equivalent scores achieved by the 23 subjects at the preimplant and 6-month intervals. The results revealed a significant improvement in receptive ($F(1,21) = 26.8$, $p < .001$) and expressive ($F(1,21) = 35.5$, $p < .001$) language over time. The mean receptive age equivalent score was 20 months ($SD = 13$) at the preimplant interval and 29 months ($SD = 13$) at the 6-month interval. Mean expressive age-equivalent scores were 19 months ($SD = 10$) at the preimplant interval and 28 months ($SD = 11$) at the 6-month interval.

Figure 1B,C shows the mean age-equivalent scores at the preimplant and 6-month intervals as a function of communication mode. There was no significant difference in age-equivalent scores between the OC and TC groups. For receptive language (Fig 1B), the oral children achieved an average age-equivalent score of 21 months ($SD = 14$) at the preimplant interval and 30 months ($SD = 16$) at the 6-month interval. The children who used TC achieved an average age-equivalent score of 20 months ($SD = 11$) at the preimplant interval and 28 months ($SD = 6$) at the 6-month interval.

When age-equivalent scores for expressive language (Fig 1C) were examined by communication mode, the OC group achieved an average age-equivalent score of 20 months ($SD = 11$) before implantation and 30 months ($SD = 13$) at 6 months after implantation. The TC group achieved an average age-equivalent score of 18 months ($SD = 11$) at the preimplant interval and 25 months ($SD = 5$) at the 6-month interval. As noted above, the difference in the mean age-equivalent scores between groups was not statistically significant.

Rate of Language Development. Rates of language

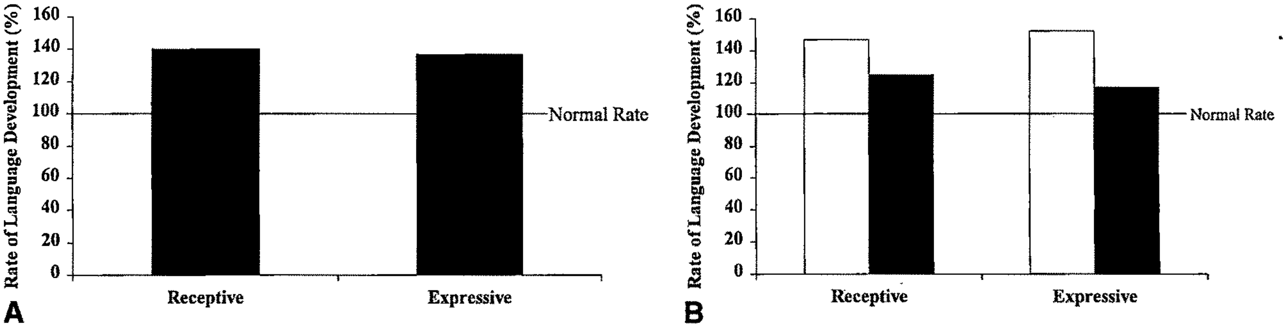


Fig 2. Rate of language development after 6 months of Clarion use. Solid horizontal line illustrates growth rate expected of normal-hearing child. A) Averaged across 23 subjects. B) Broken down by communication mode. Open bars — oral communication subjects; black bars — total communication subjects.

development for receptive and expressive scores are shown in Fig 2A. The horizontal line indicates a growth rate of 1.0, or 100% of the language growth expected of a normal-hearing child. For the 23 implanted children, the average rate of improvement for receptive language during this period was 140% (SD = 130). The average rate of improvement for expressive language was 139% (SD = 110). Thus, the mean rate of language progress for the implanted children (ie, 140%) was approximately 40% faster than expected for their normal-hearing peers of the same language age. This rate of improvement was not found to be statistically different from the normal-hearing rate, most likely because of the small sample size and the variance in performance among children.

Figure 2B shows rate of language development examined as a function of communication mode. Again, there was no significant difference between the performance of the OC and TC groups. For receptive language, the average language learning rate was 147% for the OC children and 125% for the TC children. For expressive skills, the OC children's average language learning rate was 152%, whereas the TC children's average language learning rate was 117%. Although no significant differences were found as a function of communication mode, there is a trend for faster rates of language learning by the OC children than by the children using TC. This observation must be interpreted cautiously, however, because of the small sample size in general, and the limited number of children in the TC group.

DISCUSSION

Significant increases in average age-equivalent scores in the first 6 months of Clarion use were measured in this group of 23 children. This finding is consistent with previous reports demonstrating that multichannel cochlear implants enhanced children's language development over time. The fact that these children were prelingually deaf — almost all of them congenitally deaf — is dramatic evidence of the benefit that cochlear implants provide in promoting language development in children with profound hearing impairments.

Nonetheless, even though the children showed significant increases in their language scores after implantation, their absolute language levels were still substantially delayed compared to those of their peers with normal hearing of the same chronological age — a finding also reported by others.[5,6,12] The average chronological age of these children at the 6-month interval was 46 months. In contrast, the mean language ages of these children were 29 months and 28 months for receptive and expressive skills, respectively, at the 6-month interval.

Because most deaf children at the time of implantation already are delayed in language compared to their peers with normal hearing, it is also important to document improvement relative to their preimplant skills and the time course over which the change occurs. The second analysis quantified the children's language learning rate, an aspect of development that is not adequately described when looking at age-equivalent scores alone. As stated above, a learning rate of 100% indicates a language learning rate that is equivalent to that of a normal-hearing child, that is, 1 year of language growth in 1 year. The average learning rate of 140% in the implanted children indicates a faster rate of language learning than that seen in normal-hearing children of the same language age (but who would be of younger chronological age). The importance of this finding cannot be overstated, because it indicates that these children, on average, are beginning to "catch up" to their hearing peers following implantation. Once a language delay exists, the size of that delay, that is, the gap between language age and chronological age, will remain constant if the implanted child learns at a normal-hearing rate. Consequently, in order to close the gap, the child must actually learn at a faster than normal rate, as many of these children appear to be doing.

The Reynell test was also employed in previous studies that analyzed rate of language learning in a large group of profoundly deaf, unimplanted children.[1,2,5] Data from the unimplanted children may be used as a benchmark against which to compare the children with Clarion implants. However, caution must be used when comparing those findings with data from the present study, because the demographic characteristics of the Clarion children are not matched to those of the unimplanted children. The results of those studies suggested that unimplanted children with profound hearing impairment, on average, would make 6 months of receptive and 5 months of expressive language improvement in 12 months. In contrast, the implanted children here improved at a rate equivalent to 9 months of improvement in 6 months for both receptive and expressive language — a rate faster even than that of normal-hearing children.

How is it possible that some children with cochlear implants may learn language at a faster rate than that of their peers with normal hearing? It should be kept in mind that the implanted children showed a faster acquisition rate than children of the same language age *but who are of a younger chronological age*. In the implanted children, differences in cognitive and linguistic skills — the cognitive-linguistic gap — might explain the results. This gap reflects the developmental asynchrony between nonverbal cognitive and linguistic skills in children with profound hearing impairments.[15]

Specifically, normally developing children acquire cognitive and linguistic skills concurrently, and language milestones are intimately tied to cognitive ones. However, when a significant hearing loss exists, nonverbal cognitive skills emerge normally, but linguistic development lags behind because of the sensory impairment. In other words, the deaf child has the cognitive readiness to understand and use linguistic constructs, but the sensory deficit interferes with access to these constructs. These children, although delayed in language, have more sophisticated nonverbal comprehension strategies and means of organizing their experiences than their language level indicates. In other words, their language skills are more like those of a younger child with normal hearing, even though their cognitive skills are age-appropriate. Consequently, profoundly hearing-impaired children may be able to capitalize upon underlying knowledge of the world to accelerate language learning, provided they have access to the auditory-linguistic code of English.[16] Assuming that the cochlear implant provides such linguistic access, a faster-than-normal rate of language learning may occur, because the child is both cognitively prepared for the task and has increased sensory (auditory) capacity to receive and use the language code.

The "surge" in rate of language learning experienced by many of these children is a phenomenon reported by developmental psychologists.[17] Children's development is often uneven, with spurts of growth occurring in different skill areas at various points in time. Access to new sensory information via a cochlear implant may bring about a temporary acceleration in learning within the communication domain. Piaget and Inhelder[17] described the notion of "equilibration," in which periods of accelerated growth in a cognitive skill are typically followed by less growth. Thus, the acceleration seen in the language growth of these implanted children may be temporary, given that growth in all developmental areas tends to even out over time. One would anticipate that as the implanted children's language skills approach age-appropriate levels, their rate of language improvement would slow down to a normal rate. Longitudinal follow-up is essential in order to observe whether this accelerated growth rate continues at later postimplant intervals or stabilizes.

Another hypothesis relates to the younger age at implantation in the present study group compared to previous studies. In other studies of implanted children using the Reynell test, the children's average ages at implantation were 4.9 years[5] and 5.6 years,[12] in contrast to an average age at implantation of 3.2 years for the children in the present study. This difference suggests 3 important advantages for the Clarion children. First, the extent of the language delay should be reduced, because, all factors being equal, the younger a child at time of implantation, the smaller the delay. Second, the younger child has greater neural plasticity and, it is hypothesized, greater flexibility in integrating the linguistic code made available via the device than does an older child. Third, and perhaps most important, cochlear implantation at very young ages takes advantage of the natural ability of young children to learn incidentally and to generalize across situations. This potential for incidental learning gradually decreases with increasing age. Children implanted in later years are highly dependent upon didactic instruction, a method that has been shown to be unsuccessful for true language mastery, as evidenced by adults who attempt to learn a foreign language by a strictly didactic method.

It should be noted that there was a wide range of improvement in language skills among the 23 children in the study. This variability is not unexpected, given that all implant studies, with adults or children, typically show highly variable results among subjects. In this study, some children demonstrated a rate of language learning 2 to 3 times faster than that of children with normal hearing, whereas other children showed only modest or negligible improvement within the first 6 months of implant use. Communication mode was examined as a possible factor that might contribute to the differences in performance, but this variable did not explain the variance in study outcome. Additional formal analyses were not conducted to identify the source of individual performance differences, because of the small sample size. Future studies will address this issue when data from a larger group of children are available.

One might hypothesize that users of TC would demonstrate superior language across the board, given that their visual modality is completely intact and is augmented by auditory information via the implant. In contrast, the OC learner's primary language modality, audition, is compromised in everyday listening situations, even with a cochlear implant. In fact, users of TC actually may be at a disadvantage for demonstrating language benefit from a cochlear implant, because manual forms of English do not contain the phonetic code of the language. Because the English phonetic code is auditory, children who use TC may not take advantage of this new information via their implant to the same extent as do children who use only auditory-oral cues. In addition, there may be deficiencies in the way a manual language is constructed and employed that hinder a TC child from learning aspects of auditory-based English.

It should be noted that preoperatively, the TC children in the present study had more profound hearing impairments (mean unaided PTA of 116 dB) than the OC children (mean unaided PTA of 109 dB). This difference suggests that children with more limited auditory potential with hearing aids are placed in TC programs. Thus, use of auditory-phonetic information made available through the implant may be a more challenging task for these children. Moreover, this study did not examine changes in communication mode following implantation. Clinical experience suggests the more eclectic use of manually coded English by children who demonstrate substantial progress in the acquisition of auditory-oral communication skills with their implants. Thus, over time, the difference in communication mode between the OC and TC children may become less distinct, at least in everyday communication situations.

The results of this study confirm those of previous investigations that have shown enhanced language learning in children wearing multichannel cochlear implants. The faster than normal rate of language learning seen in these prelingually deaf children who were implanted at young ages suggests a further benefit of cochlear implants: the acceleration of language learning and the possibility of eventually achieving near-normal levels of linguistic competence. Further studies should extend this research in 2 directions: to follow a larger number of children implanted with the Clarion cochlear implant and to track the time course of language development at extended postimplant intervals.

REFERENCES

1. Moeller MP, Osberger MJ, Eccarius M. Receptive language skills. ASHA 1986;23:87-91.
2. Levitt H, McGarr N, Geffner D. Development of language and communication skills in hearing-impaired children. ASHA 1978;26:140-5.
3. Boothroyd A, Geers AE, Moog JS. Practical implications of cochlear implants in children. Ear Hear 1991;12:81S-89S.
4. Dawson PW, Blamey PJ, Dettman SJ, Barker EJ, Clark GM. A clinical report on receptive vocabulary skills in cochlear implant users. Ear Hear 1995;16:287-94.
5. Robbins AM, Svirsky MA, Kirk KI. Children with implants can speak, but can they communicate? Otolaryngol Head Neck Surg 1997;117:155-60.
6. Miyamoto RT, Svirsky MA, Robbins AM. Enhancement of expressive language in prelingually deaf children with cochlear implants. Acta Otolaryngol (Stockh) 1997;117:154-7.
7. Robbins AM, Svirsky MA, Miyamoto RT. Aspects of linguistic development affected by cochlear implantation. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.
8. Quittner A, Steck JT. Predictors of cochlear implant use in children. Am J Otol 1991;12(suppl):89-94.
9. Somers M. Speech perception abilities in children with cochlear implants or hearing aids. Am J Otol 1991;12(suppl):174-8.
10. Staller S, Beiter A, Brimacombe J, Mecklenburg D, Arndt P. Pediatric performance with the Nucleus 22-channel cochlear implant system. Am J Otol 1991;12(suppl):126-36.
11. Gustason G, Zawolkow E. Signing Exact English. Los Alamitos, Calif: Modern Signs Press, 1993.
12. Reynell JK, Huntley M. Reynell Developmental Language Scales — Revised. 2nd ed. Windsor, England: NFER-Nelson Publishing, 1985.
13. Robbins AM, Osberger MJ, Miyamoto RT, Kessler KS. Language development in young children with cochlear implants. Adv Otorhinolaryngol 1995;50:160-6.
14. Muma JR. Language handbook. Englewood Cliffs, NJ: Prentice Hall, 1978.
15. Boothroyd A. Hearing impairments in young children. Englewood Cliffs, NJ: Prentice-Hall, 1982.
16. Moeller MP, McConkey AJ. Language intervention with preschool deaf children: a cognitive/linguistic approach. In: Perkins W, ed. Current therapy of communication disorders: hearing disorders. New York, NY: Thieme-Stratton, 1984:11-26.
17. Piaget J, Inhelder B. The psychology of the child. New York, NY: Basic Books, 1969.

Ann Otol Rhinol Laryngol 108:1999

SPECIFIC LANGUAGE GROWTH IN YOUNG CHILDREN USING THE CLARION® COCHLEAR IMPLANT

PRISCILLA M. BOLLARD, EDD
AMY POPP, MS
PATRICIA M. CHUTE, EDD
SIMON C. PARISIER, MD
NEW YORK, NEW YORK

General and specific language growth was evaluated in 10 children who had received the CLARION® Multi-Strategy™ Cochlear Implant during the clinical trial. The mean age at implantation was 37 months, and the children were followed for 18 months thereafter. Language comprehension and use were assessed with the Peabody Picture Vocabulary Test, the Reynell Developmental Language Scales, and mean length of utterance (MLU). The mean vocabulary scores indicated a 42-month increase in 18 months. The mean language comprehension increased from 20.4 to 40.8 months, and language use increased from 21.5 to 38.1 months. The mean MLU increased from 1.8 words to 4.8 words during the test period. Results indicated the children learned language at the same rate as their hearing peers of the same language age (except for vocabulary, which was faster), but retained a language delay relative to their hearing peers of the same chronological age.

KEY WORDS — cochlear implant, prelinguistic deafness, specific language growth.

INTRODUCTION

Language development in normal-hearing children has been studied extensively. In a normal child, language comprehension and expression develop in an orderly sequence that commences with preverbal vocalizations that develop into gestural behaviors, "meaningful utterances," words, and finally sentences.[1,2]

Similar studies have documented the development of language in young deaf children.[3-5] Deaf children reportedly communicate less frequently and less precisely than hearing children of the same age.[6] Moreover, they acquire receptive vocabulary at approximately half the rate of hearing children, independent of their communication mode (sign or oral).[7-9]

More complex language skills also are affected in deaf children. They have more difficulty generating morphological forms and verb endings.[10] Interestingly, the same difficulty understanding and using verb forms has been observed in normal-hearing children with specific language impairment.[11] This similar finding in both hearing- and language-impaired children raises the possibility that grammar and syntax are more difficult to acquire than vocabulary. Deaf children use more nouns and articles but use prepositions, quantifiers, and indefinite pronouns less frequently. Also, the accuracy of sentence structure decreases with greater hearing loss.[12-14] On a sentence imitation task, more than half the deaf subjects simplified sentences and reproduced sentences with omissions, incorrect inflectional endings, aberrant word order, or inappropriate substitutions.[5]

Thus, oral language acquisition is highly dependent upon what the deaf child can hear. Speech perception studies in deaf children have shown that the ability to process vocal contrasts such as voicing, pitch, and intonation decreases with increasing hearing loss.[15] Processing of these features in addition to vocabulary is essential for accurate comprehension of words and sentences. Deficits in suprasegmental processing have been attributed to the lack of "auditory capacity," which prevents effective auditory monitoring and auditory feedback for the correction of errors. It also precludes learning through incidental listening.[16]

Cochlear implants have provided deaf children with a means of accessing the auditory information that is essential for language development. Specifically, a cochlear implant provides high-frequency and temporal information that is not available from a conventional hearing aid. Children with cochlear implants have exhibited better speech perception[17,18] and increased speech production skills in terms of intelligibility and the number of vowels and consonants produced than children using hearing aids.[19] They also show an increased use of nonfunctional words, grammatical morphemes, and incidental learning.[20] Recognition and production of suprasegmental features — syllabification, stress, and intonation — also are superior to those of nonimplanted deaf children of the same age.[21] Furthermore, implanted children may learn language at the same rate

---

From Lenox Hill Hospital, New York, New York.
CORRESPONDENCE — Priscilla M. Bollard, EdD, Lenox Hill Hospital, 186 E 76th St, 2nd Floor, New York, NY 10021.

as hearing children, even though they retain an overall language delay[22] (also Robbins et al, this volume, pp 113-8).

Most of the new candidates for cochlear implants are very young children who will be able to take maximum advantage of the auditory information provided by the device during the prime language-learning years. However, the assessment of these very young children has been difficult because of their general immaturity, the paucity of objective tests that can be used below 3 years of age, and their limited language skills. Although a variety of assessment tools have been used by other researchers to evaluate very young children[23,24] (also Robbins et al, this volume, pp 113-8), little data is available on language development in very young implanted children. In published reports, either the test materials have not been standardized, or the children were implanted at older ages. (A comprehensive review of research on preschool language tests that can be used with very young children has been written by Nicholas and Geers.[6])

Therefore, the purpose of this study was to examine language growth in children implanted at a very young age (mean age 3.1 years) and to compare the results to published results on children implanted at an older age, nonimplanted deaf children who use hearing aids, and children with normal hearing. It was hypothesized that general language growth would be similar to or better than that in children implanted at an older age, because of the shorter period of auditory deprivation prior to implantation. In addition, the children were expected to demonstrate more rapid development of vocabulary and sentence length than their deaf nonimplanted counterparts.

METHODS

Subjects. Ten children who were implanted with the CLARION® Multi-Strategy™ Cochlear Implant were selected for the study out of the first 13 children to receive the device in the clinical trial. Three children were eliminated because of insufficient test data. All 10 children had congenital deafness of unknown cause. Before implantation, their mean unaided pure tone average hearing thresholds were 107 dB hearing level (HL) in the right ear and 110 dB HL in the left ear. All but 1 child had no measurable unaided hearing above 2,000 Hz. The mean age at implantation was 3.1 years (37 months; range 2.2 to 4.6 years). Nine children were implanted in the right ear, and 1 child received the implant in the left ear. All children were programmed in the Continuous Interleaved Sampler (CIS) monopolar mode. Program optimization and usage was monitored on a routine basis by the implant facility and the school. Regular reports from teachers and parents in conjunction with perceptual measures obtained by the implant center were used to monitor the benefit obtained from the implant.

All children had normal intelligence and were enrolled in excellent preschool settings. Seven children used oral communication, and 3 children used total communication. Workshops for parents and educators were presented by the implant center staff on auditory-aural enhancement techniques to facilitate oral language learning after implantation.

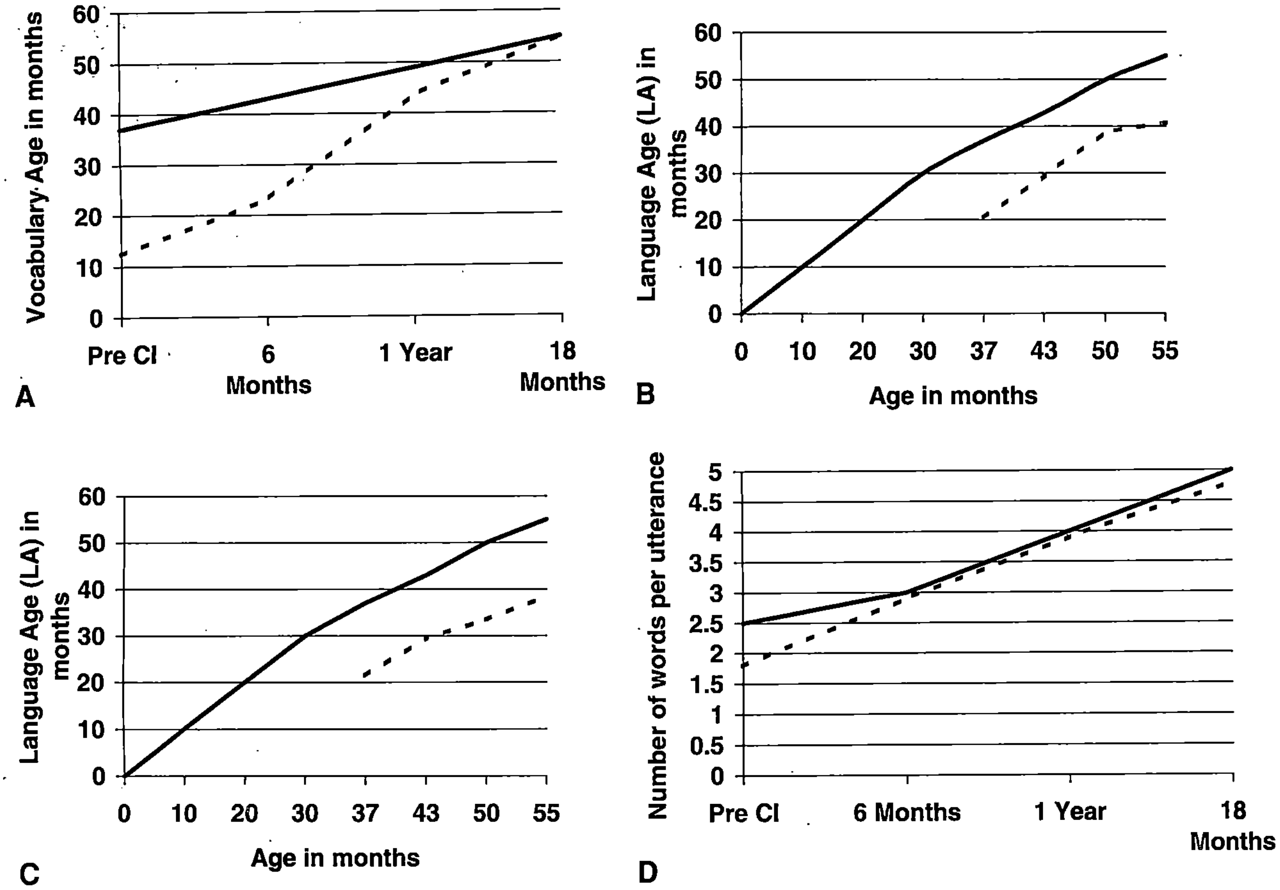
Test Procedures. Three procedures were used to assess language skills: the Reynell Developmental Language Scales (RDLS),[25] the Peabody Picture Vocabulary Test (PPVT),[26] and calculation of the mean length of utterance (MLU). Testing was performed via each child's preferred mode of communication: either total communication (signed English system plus speech and audition) or oral communication (audition, speech, and lipreading). The children were tested before implantation and at 6-month intervals thereafter to 18 months postimplantation.

The RDLS has been used extensively with both the hearing and hearing impaired–deaf populations, and was designed to evaluate language skills in young children from 1 to 8 years of age. The RDLS has many advantages, including rapid administration and scoring, both receptive and expressive language forms, and age-appropriate objects that are fun for young children to handle, and it can be administered with either signed or spoken English. In the RDLS:Receptive Language scale, comprehension is evaluated through watching children manipulate objects when the examiner presents stimulus sentences. The RDLS:Expressive Language scale requires children to provide a spoken or signed response.

The PPVT is a 4-choice picture test that also can be administered rapidly and has been found to be a reliable and valid test of lexical and semantic skills in deaf children.[25] The MLU was calculated from the expressive language sample elicited during administration of the expressive language section of the RDLS. In studies of hearing children, a high correlation is found between the MLU and the stages of language development and the use of specific word types.[1,2]

RESULTS

The Figure, A, presents the receptive vocabulary PPVT data. Before implantation, many of the children did not know any of the vocabulary in the PPVT and were assigned a score of zero on the initial evaluation. A score of zero does not necessarily mean that the children did not know any words, but only that



Comparisons between measures for implanted children (broken lines; n = 10; n = 6 for 18-month point) and normal-hearing children of same language age. A) Vocabulary growth, as measured by Peabody Picture Vocabulary Test. B) Receptive language growth, as measured by Reynell Developmental Language Scales. C) Expressive language growth, as measured by Reynell Developmental Language Scales. D) Mean length of utterance.

they did not know the words in the test. The final 18-month data were obtained for only 6 children. Four children missed their 18-month evaluation appointments because of illness.

On the PPVT, the children showed a mean language age (LA) of 12.4 months prior to implantation. At the end of 18 months, they reached a mean LA of 55 months and had equaled their hearing peers of the same chronological age in vocabulary acquisition. The difference in LA between the implanted children and hearing children was greatest prior to implantation (24.6 months) and decreased throughout the testing period (18.5 months at 6 months, 5.4 months at 12 months, and no difference at 18 months). Notably, the fastest acquisition of vocabulary occurred during the first 6 months after implantation.

The data for the 4 children who missed the 18-month test data were assessed to determine if their scores would have biased the study positively or negatively. Those 4 children were all high language achievers at the earlier 3 test intervals, so the final results might have been even higher if their 18-month scores had been included.

The RDLS:Receptive Language results are shown in the Figure, B. This test assessed the ability to understand age-appropriate language within sentences. The mean preimplant LA was 20.4 months, and the mean 18-month LA was 40.8 months. These data represent a 20-month growth in receptive language skills in 18 months. This pattern parallels the language growth rate of hearing children of the same language age and is similar to results obtained by Robbins et al[22] with slightly older implanted children.

Although the rate of receptive language acquisition paralleled that of normal children of the same LA, the absolute level of language remained below that of normal-hearing children of the same chronological age. Before implantation, the children in this study were approximately 17 months behind normal children in language level. After 18 months, even though they learned language at the same rate as their hearing peers of the same LA, they had not closed the gap in language level with their age-matched normal-hearing peers.

Expressive language growth was similar to receptive language acquisition but not quite as rapid (see Figure, C). The mean LA prior to implantation was 21.5 months, increasing to 38.5 months at 18 months after implantation. Therefore, the change in score was 17 months over the 18-month test period, indicating that the implanted children were acquiring expressive language skills at the same rate as their hearing cohorts of the same LA. Nonetheless, the expressive language delay they demonstrated before implantation was still evident at the end of the testing period as compared to their age-matched hearing peers (15.5 months preimplantation and 16.5 months at 18 months postimplantation).

The MLU data are shown in the Figure, D. The implanted children began at a 1.8-word level before implantation and ended at the 4.8-word level 18 months after implantation. The majority of their responses were single- or 2-word utterances, and sentences were simple in construction. These MLU values indicate a steady increase in the length of sentences used, but a slight falling-off at the 18-month point.

DISCUSSION

Several important results have emerged from this study of vocabulary and language growth in children using the Clarion cochlear implant. First, the 10 children in this study showed vocabulary growth of almost twice the rate of hearing children of the same LA. There are many reasons for this rapid growth, including the increased auditory capacity provided by the cochlear implant, the increase in incidental listening provided by the cochlear implant, the younger age at implantation, home and school emphasis on labeling and naming, and the rapid acquisition of single words that occurs developmentally at this stage. In fact, previous studies with children implanted at an older age have not shown such rapid acquisition of vocabulary immediately after implantation.[22] Nonetheless, it should be remembered that in spite of the remarkable scores on the PPVT, the children still demonstrated substantial gaps in their knowledge of words compared to normal-hearing age-matched children.

Second, the implanted children exhibited the same rate of growth in language as their hearing peers of the same LA — an encouraging result. Both receptive and expressive language skills were developing along normal developmental lines, with a few exceptions. Notably, these results are similar to those of Robbins et al[22] and indicate that implanted children can begin to acquire language at a normal rate. In contrast, the nonimplanted deaf children in the Robbins et al study acquired receptive language at approximately half the rate of their hearing peers. Nonetheless, the absolute language delays (re normal-hearing children) exhibited by the implanted children at the beginning of the study were retained at the end of 18 months.

Third, the MLU data indicate that the implanted children used shorter sentences than their hearing peers. The use of shorter sentences may be attributed to a variety of factors, including difficulty making themselves understood, difficulty acquiring grammatical forms, and problems associated with word order and auditory memory. Previous research has shown that many deaf children do not receive the same quality or quantity of auditory modeling and practice from their families or educational programs as hearing children.[27] Frequently, insufficient attention has been paid to developing auditory awareness, auditory recall, auditory recognition and production of suprasegmental features, auditory recognition and repetition of linguistic and nonlinguistic features of various lengths, and derivation of meaning through stress, pause, and context within a variety of natural settings. Much less time and energy is devoted to developing these auditory skills than to vocabulary acquisition. In contrast, the hearing child is provided with many opportunities through singing, rhyming, auditory games, oral reading, and conversation to expand the ability to understand and use longer language units.

Fourth, clinical observations suggested that the implanted children began to rely principally on their hearing for language comprehension after 18 months of implant use. The increase in the use of audition for comprehension and monitoring purposes is positive and suggests that incidental listening is occurring among the cochlear-implanted children.

Taken together, these results indicate that language delays resulting from auditory deprivation cannot be made up completely in 18 months. Unfortunately, the deaf child must catch up with his hearing peers as quickly as possible before the demands of language and academic achievement become too great. The key to overcoming the language delay appears to lie in the "auditorization" process, which is a strong argument for early implantation of deaf children. Early implantation decreases the period of auditory deprivation and provides more time during the preschool years to make up language delays or disorders. Along with implantation, an enriched auditory language environment is recommended both at home and in school to facilitate the acquisition of age-appropriate oral language skills as rapidly as possible.

REFERENCES

1. Bloom L, Lahey M. Language development and language disorders. New York, NY: John Wiley and Sons, 1978.

2. Brown R. A first language, the early stages. Cambridge, Mass: Harvard University Press, 1973.

3. Osberger MJ. Language and learning skills of hearing impaired students. ASHA Monogr 1986;23:116-23.

4. Sarachan-Deily A, Love R. Underlying grammatical rule structure of the deaf. J Speech Hear Res 1974;17:689-98.

5. Geers AE. Comparing implants with hearing aids in profoundly deaf children. Otolaryngol Head Neck Surg 1997;117: 150-4.

6. Nicholas JG, Geers AE. Communication of oral deaf and normally hearing children at 36 months of age. J Speech Hear Res 1997;40:1314-27.

7. Moog JS, Geers AE. Grammatical analysis of elicited language — simple sentence level. 2nd ed. St Louis, Mo: Central Institute for the Deaf, 1985.

8. Robbins AM, Svirsky M, Kirk KI. Children with implants can speak, but can they communicate? Otolaryngol Head Neck Surg 1997;117:155-60.

9. Robbins AM, Osberger MJ, Miyamoto RT, Kessler KS. Language development in young children with cochlear implants. Adv Otorhinolaryngol 1994;50:160-6.

10. Kretschmer RR, Kretschmer LW. Language development and intervention with the hearing impaired. Baltimore, Md: University Park Press, 1972:112.

11. Conti-Ramsden G, Jones M. Verb use in specific language impairment. J Speech Hear Res 1997;40:1298-313.

12. Geers AE, Moog JS. Effectiveness of cochlear implants and tactile aids for deaf children. Volta Rev 1994;96:131-48.

13. Brannon J. Linguistic word classes in the spoken language of normal, hard of hearing and deaf children. J Speech Hear Res 1968;11:279-87.

14. Brannon J, Murry T. The spoken syntax of normal, hard of hearing and deaf children. J Speech Hear Res 1966;9:604-10.

15. Boothroyd A, Geers AE. Practical implications of cochlear implants in children. Ear Hear 1991;12:81S-89S.

16. Brackett D, Zara C, Peters K. Incidental listening skills in children with cochlear implants. Presented at the American Academy of Audiology, Salt Lake City, Utah, April 18-21, 1996.

17. Waltzman SB, Cohen NL, Shapiro WH. Effects of cochlear implantation on the young deaf child. Adv Otorhinolaryngol 1995;50:125-8.

18. Parisier SC, Chute PM, Hellman SA. The use of cochlear implants for profound hearing loss. Surg Rounds 1989(June);15-20.

19. Tobey E, Pancamo S, Staller S, Brimacombe J, Beiter A. Consonant production in children receiving a multichannel cochlear implant. Ear Hear 1991;12:23-31.

20. Brackett D, Zara C, Peters K. Grammatical morpheme recognition in children with cochlear implants. Presented at the American Academy of Audiology, Salt Lake City, Utah, April 18-21, 1996.

21. Bollard PM, Chute PM, Parisier SC. Prosody development in children with cochlear implants 2 to 5 years of age. Presented at the American Academy of Audiology, Salt Lake City, Utah, April 18-21, 1996.

22. Robbins AM, Svirsky MA, Miyamoto RT. Aspects of linguistic development affected by cochlear implantation. Presented at the Vth International Cochlear Implant Conference, New York, NY, May 1-3, 1997.

23. Osberger MJ. Cochlear implantation in children under the age of two years: candidacy considerations. Otolaryngol Head Neck Surg 1997;117:145-9.

24. Tait DM, Lutman ME. Comparison of early communicative behavior in young children with cochlear implants and with hearing aids. Ear Hear 1994;14:378-89.

25. Reynell JK, Huntley M. Reynell Developmental Language Scales — Revised. 2nd edition. Windsor, England: NFER Publishing, 1985.

26. Dunn L, Dunn L. Peabody Picture Vocabulary Test (PPVT). Circle Pines, Minn: American Guidance Corp, 1981.

27. Collins J. Communication between deaf children of preschool age and their mothers [Dissertation]. Pittsburgh, Pa: University of Pittsburgh, 1969.

Ann Otol Rhinol Laryngol 108:1999

META-ANALYSIS OF PEDIATRIC COCHLEAR IMPLANT LITERATURE

ANDRÉ K. CHENG, MD
GINGER D. GRANT, MS
JOHN K. NIPARKO, MD
BALTIMORE, MARYLAND

We analyzed published reports of the effect of age at implantation and the cause of and age at onset of deafness on speech perception benefit in children with cochlear implants, and compared these results with those of unreported trials of multichannel cochlear implants. Combining data from published and unpublished patient series was constrained by differences in test protocols between studies, but was made feasible by employing a meta-analysis in which data were converted into an ordinal classification scale that represented levels of communicative benefit. Results showed that more rapid gains in speech perception are associated with earlier age at implantation, and that speech perception results are independent of cause of or age at onset of deafness after 1 year of implant use. Moreover, with minor exceptions, there was no statistical difference between published and unpublished data, thereby indicating no publication bias in the literature. A meta-analytic approach is useful because it can clarify the quality of reported data and the direction of future research and, hopefully, foster collaboration in conducting and reporting future research. A standardized approach to reporting results in children is advised in order to produce a balanced interpretation of implant benefit and to facilitate wider understanding and dissemination of study conclusions.

KEY WORDS — children, cochlear implant, speech perception.

INTRODUCTION

Despite an extensive body of evidence documenting communicative benefit of cochlear implantation in profoundly deaf children, published results have engendered skepticism in some readers. For example, it is asserted that prelingually implanted deaf children "cannot" acquire open-set speech recognition and that testing of these children harbors "protocol bias."[1]

To address such concerns and to provide a systematic review of the relevant literature, we performed a meta-analysis of reports on speech recognition in children with cochlear implants. A meta-analysis provides a structured review and integration of published results across studies. Meta-analytic methods are particularly useful when large randomized control trials are impractical, when sample sizes of individual studies are too small, and when studies disagree. In contrast to an individual study, a meta-analysis facilitates sampling a larger number of subjects across a broader cross section of patients undergoing the same treatment or intervention. When aggregate data can be pooled and compared, stronger conclusions may be drawn about effectiveness. Moreover, the results can provide information on both known and unknown determinants of treatment efficacy.

Nonetheless, even rigorously performed meta-analyses may be subject to publication biases.[2] For example, studies with negative results are less likely to be published, and meta-analyses of published data are typically unblinded.[3] Published data thus may misrepresent an intervention's impact by systematically failing to report certain outcomes. Early studies based on small subject populations may be published earlier and therefore are overly optimistic relative to less favorable trials that report inconclusive or negative results.

A strategy that might address the possibility of publication bias would be to compare aggregate data from the literature with previously unreported independent patient data. This comparison may identify discrepancies between published and unpublished studies or between individual data sets that may reflect methodological error or bias. Consequently, this paper reports a meta-analysis that compares the effect of 1) age at implantation and 2) the cause of or age at onset of deafness on speech perception in implanted children, using both published and unpublished data. These 2 variables were selected because previous research has shown that they have a significant effect on postimplant performance.[4-7] It should be noted that causation is confounded by age at onset of deafness. This confounder exists because congenital deafness occurs by definition prelingually, whereas acquired deafness resulting from, for example, meningitis, can occur prelingually or postlingually.

METHODS

Data Extraction. A MEDLINE search of abstracts published since 1966 using the key words "cochlear

---

From the Department of Otolaryngology–Head and Neck Surgery, The Johns Hopkins University, Baltimore, Maryland.
CORRESPONDENCE — John K. Niparko, MD, Dept of Otolaryngology–Head and Neck Surgery, The Johns Hopkins University, PO Box 41402, Baltimore, MD 21203-6402.

implant" and "cochlear implants" yielded 1,916 citations. Additional searches using manufacturer names as key words and subcategories of "deafness" yielded no additional citations. Clinical results were reported in 577 (30.1%) of the citations. Speech perception was the subject matter in 421 (22.0%) of them, 218 of which pertained to children (under 18 years of age). Patient data with at least 1 year of follow-up were reported in 44 of the articles. Consequently, those 44 articles provided the published results for the analysis.

Unpublished results with at least 1 year of follow-up were obtained from clinical trial data submitted to the US Food and Drug Administration in premarket applications submitted by Cochlear Corporation in 1990 (n = 107) and by Advanced Bionics Corporations in 1997 (n = 53). In addition, data from 42 implanted children from the Johns Hopkins Listening Center program with at least 1 year of follow-up were included in the unpublished data set.

The 44 published papers provided data on speech perception after implantation with multichannel cochlear implants (n = 1,904 children). However, many variables confounded direct comparison of results between studies. Those variables included the use of different speech perception tests (because the children's ages and developmental stages differed), research design, patient factors (eg, age at implantation, age at onset of deafness, cause of deafness), treatment variables (device implanted, number of electrodes inserted into cochlea, speech processing strategy), and differences in data collection (age at testing, test scoring protocol, frequency of testing).

Therefore, we analyzed data from a subgroup of the 44 papers that provided individual patient results that could be pooled and analyzed to examine the 2 variables of interest: age at implantation and cause/age at onset of deafness. Eleven articles provided speech perception data with respect to age at implantation.[4,5,8-15] Nine articles provided data with respect to cause/age at onset of deafness.[5-7,14-19]

Of the 11 articles reporting age-at-implantation data, 3 articles were omitted because they reported duplicate results. Of the remaining 8 reports, 3 reported patient data by age group. The age groupings were different in the 3 articles. V. Meyer et al (unpublished observations) compared ages 2 to 4 years versus 4 to 7 years versus 7 years and older; Waltzman et al[4] compared ages 2 to 3 years versus 3 to 5 years; and Gantz et al[14] compared ages 2 to 5 years versus 5 to 8 years versus 8 years and older. In the other 5 papers, individual patient data were not presented. The only extractable data were an average score (X) at an average age at implantation (Y) for a specified number of subjects (Z). Of the 9 articles reporting patient data with respect to cause/age at onset of deafness, 3 articles were omitted because they reported duplicate results, leaving 6 articles with usable data.

In contrast to the published data, individual patient data from the unpublished trials were collated and analyzed easily for the 2 variables of interest.

Data Synthesis. The literature reported results on 22 different tests of receptive benefit in spoken communication. To provide a common measure to integrate results across studies, each test percentage score was translated into a speech perception categories ordinal score (Fig 1[20]). The speech perception categories provide an ordinal scale for 5 levels of speech perception that range across simple detection, pattern perception, inconsistent and consistent closed-set word recognition, and open-set word recognition. For example, a child who attained a 70% score on the NU-CHIPS word test was assigned an ordinal score of 4. A sixth category was added to accommodate scores on open-set speech recognition tests that exceeded the levels associated with older cochlear implant designs. This type of ordinal scale is representative of the range of spoken communication skills exhibited by implanted children in an educational setting.

We encountered a number of speech perception tests not incorporated in the original speech perception categories and assigned them ordinal scores appropriately (eg, Iowa and Hannover speech perception tests). Study results then were compared to determine the impact of age at implantation and cause/age at onset of deafness on speech perception performance.

Data Analysis. The conversion of published and unpublished results into ordinal categories rescaled continuous measures to ordinal data sets. This conversion provided a less detailed representation of the results, and introduced statistical constraints so that

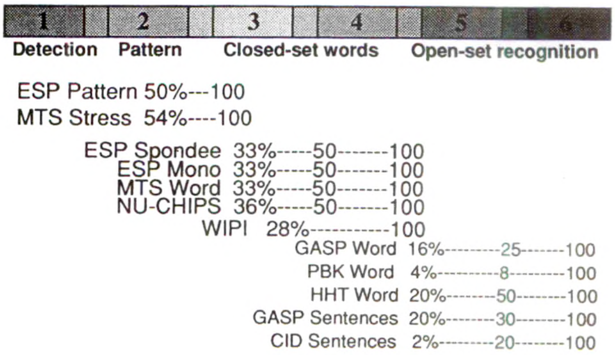

1
2
3
4
5
6
Detection
Pattern
Closed-set words
Open-set recognition
ESP Pattern 50%---100
MTS Stress 54%----100
ESP Spondee 33%-----50-------100
ESP Mono 33%-----50-------100
MTS Word 33%-----50-------100
NU-CHIPS 36%-----50-------100
WIPI 28%-----------100
GASP Word 16%---------25-------100
PBK Word 4%----------8---------100
HHT Word 20%--------50--------100
GASP Sentences 20%--------30--------100
CID Sentences 2%---------20--------100

Fig 1. Speech perception categories assigned to scores on different tests of receptive speech perception in children (information from Geers and Moog[20]).

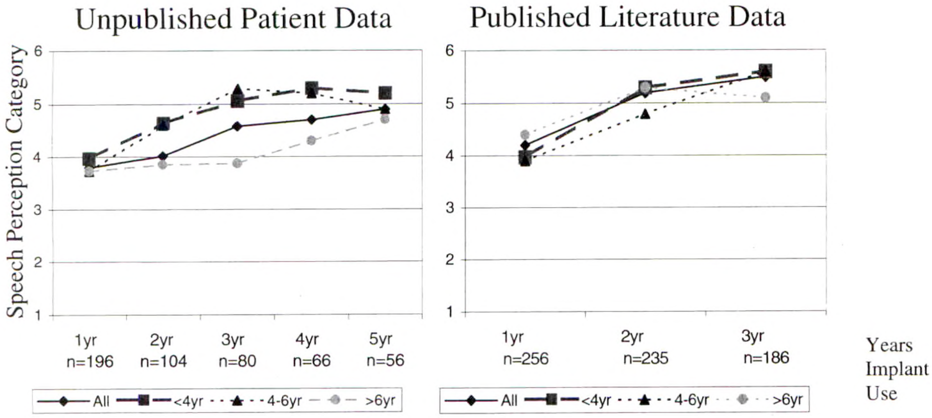


Fig 2. Mean speech perception category attained as function of years of implant use, stratified by age at implantation. Curves on left and right represent unpublished and published data sets, respectively. Changes in performance category should be considered in context of different populations sampled at each time point.

parametric analysis could not be applied. Therefore, the ordinal data were compared by the nonparametric Wilcoxon test statistic.[21] The disadvantage to this nonparametric analysis is that there is less statistical power when differences between subject groups are found. Published and unpublished scores were compared for speech perception results as a function of age at implantation and cause/age at onset of deafness.

RESULTS

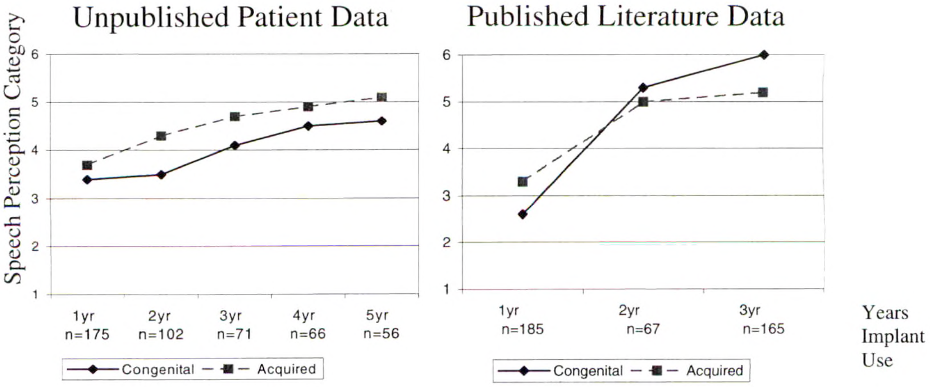
Age at Implantation. There is concordance between the data reported in the literature and the data from unpublished clinical trials, arguing against publication bias in the pediatric cochlear implantation field (Fig 2). The 1 exception is the reporting of higher scores in the literature for the oldest age group (>6 years old) after 2 and 3 years of implant use. Notably, of the 8 published articles analyzed, 6 concluded that the earlier the age at implantation, the better the results. A number of articles, however, stated this conclusion (or the opposite conclusion) without presenting any data. There was no statistical difference between subjects implanted at different age groups in the literature, whereas the oldest age group attained significantly lower scores after 2, 3, and 4 years of implant use in the unpublished data set. There also seems to be no plateau of benefit over time, no matter what the age at implantation. This pattern is different from the pattern reported for postlingually deafened adults, in whom earlier age at implantation correlates with better speech perception results, but in whom those results plateau.[22]

In general, pooling the results revealed no statistical differences in scores between the published and unpublished data for cause/age at onset of deafness. In both published and unpublished data sets, there seems to be no difference between subjects deafened from meningitis compared to other acquired causes of deafness. There was 1 minor exception. Unpublished data show that congenitally deafened children score lower than children with acquired deafness during the first year after implantation (Fig 3). However, the difference in performance diminishes over time, and is not statistically significant 1 year after implantation. The published data, on the other hand, show higher scores for congenitally deafened children after 2 to 3 years of implant use. Although this minor difference between published and unpublished data was significant, the analysis was influenced by the fact that the published data set was recent and the unpublished data set was older.

DISCUSSION

For both age at implantation and cause/age at onset of deafness, there is concordance between the published data and the unpublished clinical trial data,

Fig 3. Mean speech perception category as function of years of implant use, stratified by cause of deafness. Solid line indicates congenital deafness; dashed line indicates acquired deafness. Curves on left and right represent unpublished and published data sets, respectively. Changes in performance category should be considered in context of different populations sampled at each time point.



which indicates that there is no publication bias. The overall analysis of the benefits of cochlear implantation in children shows the following.

1. Open-set speech understanding was observed in over half of the reported implanted subjects within 2 years after implantation.

2. Initial trends suggest that earlier implantation is associated with a greater trajectory of gains in speech recognition.

3. There is no plateau in speech perception benefit over time.

4. Differences in performance between congenital and acquired causes of deafness diminish over time and are not statistically significant.

5. Comparisons of published and unpublished data do not indicate any systematic publication bias.

Importantly, current clinical results show little difference from published results, thereby refuting the notion of publication bias in the pediatric cochlear implantation literature. However, because published data are pooled from literature representing an era of clinical practice that has since rapidly evolved (eg, younger age at implantation, technological improvements in implants), the inclusion of older reports may increasingly misrepresent, and underestimate, the current benefit of childhood cochlear implantation.

Standardized reporting methods offer the best means of exploring overall treatment effects by cumulative meta-analytic methods. Unfortunately, those methods cannot be applied to most pediatric cochlear implant reports to date. In order to eliminate the need for rescaling data for the purposes of combining results, our recommendation is for future articles to report or make available individual patient data including age at implantation, cause/age at onset of deafness, and speech perception scores yearly, starting at a minimum of 1 year after implantation. Test protocols, which necessarily vary widely across pediatric populations, should be described explicitly.

The ability to perform true meta-analyses requires cooperation between clinicians who have invested considerable resources in their work. Adopting a unified approach to data reporting can provide a collective pool of data that can guide future treatment and research. Meta-analyses of collective data are important, because they can be used by health care providers to make decisions about appropriate intervention.

ACKNOWLEDGMENTS — We gratefully acknowledge the assistance of Mary Joe Osberger, PhD, Steven Staller, PhD, Nancy K. Mellon, Karin E. Young, MA, and Hyla Dobaj, MA, in compiling the independent patient data sets used for comparisons in this report.

REFERENCES

1. Lane H. Letter to the editor. Am J Otol 1995;16:393-9.

2. Jeng GT, Scott JR, Burmeister LF. A comparison of meta-analytic results using literature vs individual patient data: paternal cell immunization for recurrent miscarriage. JAMA 1995; 274:830-6.

3. Oxman AD, Clarke MJ, Stewart LA. From science to practice: meta-analyses using individual patient data are needed. JAMA 1995;274:845-6.

4. Waltzman SB, Cohen NL, Gomolin RH, et al. Perception and production results in children implanted between 2 and 5 years of age. Adv Otorhinolaryngol 1997;52:177-80.

5. Waltzman SB, Cohen NL, Gomolin RH, Shapiro WH, Ozdamar SR, Hoffman RA. Long-term results of early cochlear implantation in congenitally and prelingually deafened children. Am J Otol 1994;15(suppl):9-13.

6. Osberger MJ, Todd SL, Berry SW, Robbins AM, Miyamoto RT. Effect of age at onset of deafness on children's speech perception abilities with a cochlear implant. Ann Otol Rhinol Laryngol 1991;100:883-8.

7. Staller SJ, Beiter AL, Brimacombe JA, Mecklenburg DJ, Arndt P. Pediatric performance with the Nucleus 22-channel cochlear implant system. Am J Otol 1991;12:126-36.

8. Uziel AS, Reuillard-Artieres F, Mondain M, Piron J-P, Sillon M, Vieu A. Multichannel cochlear implantation in prelingually and postlingually deaf children. Adv Otorhinolaryngol 1993;48:187-90.

9. Frachet B, Minvielle E, Chouard CH, et al. Final report on 1992-1993 children's cochlear implant at the Assistance Publique-Hopitaux de Paris. Adv Otorhinolaryngol 1995;50:102-7.

10. Meyer V, Bertram B, Lenarz T. Performance comparisons in congenitally deaf children with different ages of implantation. Adv Otorhinolaryngol 1995;50:129-33.

11. Shea JJ, Domico EH, Lupfer M. Speech perception after multichannel cochlear implantation in the pediatric patient. Am J Otol 1994;15:66-70.

12. Tyler RS, Summerfield AQ. Cochlear implantation: relationships with research on auditory deprivation and acclimatization. Ear Hear 1996;17(suppl):38S-50S.

13. Miyamoto RT, Osberger MJ, Todd SL, et al. Variables affecting implant performance in children. Laryngoscope 1994; 104:1120-4.

14. Gantz BJ, Tyler RS, Woodworth GG, Tye-Murray N, Fryauf-Bertschy H. Results of multichannel cochlear implants in congenital and acquired prelingual deafness in children: five-year follow-up. Am J Otol 1994;15(suppl):1-7.

15. Waltzman S, Cohen N, Shapiro W. Effects of cochlear implantation on the young deaf child. Adv Otorhinolaryngol 1995;50:125-8.

16. Bertram B, Lenarz T, Meyer V, Battmer RD, Hartrampf R. Performance comparisons in postmeningitic prelinguistic and congenitally deaf children. Adv Otorhinolaryngol 1995;50:134-8.

17. Uziel AS, Reuillard-Artieres F, Sillon M, et al. Speech perception performances in prelingually deafened children with the Nucleus multichannel cochlear implant. Adv Otorhinolar-

yngol 1995;50:114-8.

18. Miyamoto RT, Osberger MJ, Robbins AM, Myres WA, Kessler K. Prelingually deafened children's performance with the Nucleus multichannel cochlear implant. Am J Otol 1993; 14:437-45.

19. Waltzman SB, Cohen NL, Shapiro WH. Use of a multichannel cochlear implant in the congenitally and prelingually deaf population. Laryngoscope 1992;102:395-9.

20. Geers AE, Moog JS. Predicting spoken language acquisition of profoundly hearing impaired children. J Speech Hear Disord 1987;52:84-94.

21. Fisher LD, van Belle G. Biostatistics. A methodology for the health sciences. New York, NY: John Wiley & Sons, 1993:310-21.

22. NIH Consensus Panel on Cochlear Implants. JAMA 1995;274:1955-61.